The Journal of
NERVOUS and MENTAL DISEASE

VOL. 128, NO. 6
June, 1959
SERIAL NO. 919

GENERAL PHYSIOLOGY AND PHARMACOLOGY OF SYNAPSES AND SOME IMPLICATIONS FOR THE MAMMALIAN CENTRAL NERVOUS SYSTEM[1]

HARRY GRUNDFEST, PH.D.[2]

EVOLUTION OF EXCITABLE MEMBRANES

Functional differentiation of excitable cells. There is considerable justification (*cf.* 68) for the view that the nervous system evolved by elaboration of a primitive receptor-effector cell (Figure 1). However, included in this view has been the tacit assumption that the functions of receptor, effector, and correlational activities in the more advanced Metazoa became parcellated among different types of specialized cells as sense organs, the nervous system, muscles and glands. Recent evidence contradicts this assumption (40, 46, 47). While each cell type of the excitable tissues appears to play a specialized role, sensory receptor, correlational neuron, or effector unit, in reality each cell retains and utilizes both its primitive receptor-effector structures and their activities. Many, but not all, excitable cells have gained an additional component, a correlational structure capable of generating and conducting impulses. This presumably was made necessary by the extension of nerve cells and muscle fibers in Metazoa. Gland cells, some receptors, and some kinds of muscle fibers, in which conduction need play no role, do not have this component. It is also absent in the electroplaques of all the marine electric fishes, but probably as an evolutionary loss of the conductile membrane of their precursors, striated muscle fibers.

Components of the cell membrane. Each neuron may be generalized (Figure 2) into a structure with three components[3]. They are functionally distinct, as has been revealed by studies on a large variety of single excitable cells. These data, from many laboratories, and a new theoretical formulation (35, 37–40, 44–47) have to a considerable extent clarified the characteristics of the different components, the mode of their in-

[1] Based on lectures in 1958–1959 at the University of Chicago; Vanderbilt University, Nashville; London and Cambridge Universities; The Charles University, Prague; and The Sorbonne. Work from the author's laboratory is supported in part by grants from the Muscular Dystrophy Associations of America, Inc., National Institute of Neurological Diseases and Blindness (B-389 C3), National Science Foundation (NSF G-2030) and United Cerebral Palsy Research Foundation. The studies on physiology and pharmacology of the mammalian central nervous system are in collaboration with Professor D. P. Purpura, Department of Neurological Surgery, a scholar of the Kenny Foundation. Dr. Purpura also received support from the National Institute of Neurological Diseases and Blindness (B-1312) and the Paul Moore Neurosurgical Research Fund.

[2] Department of Neurology, College of Physicians and Surgeons, Columbia University, New York.

[3] Neurons offer a clear-cut functional identification of the three membrane components. The effector component in muscle fibers presumably is the site of transfer of electrical activity into contraction (*cf.* 56). The summation of e.m.f.'s from individual cells to produce high voltage pulses is the effector function of electroplaques. This is made possible by several varieties of modification in membrane properties of different kinds of electroplaques (5, 6, 39). The modified membrane structures therefore may be regarded as the effector component.

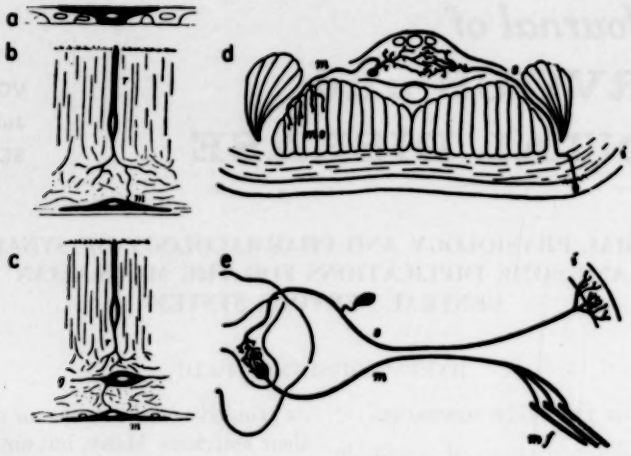


FIG. 1. Evolution of neuro-effector apparatus according to Parker (68). *a*. Primitive form, combined receptor-effector of pore in sponge. *b*. Double element, receptor (r) and effector muscle (m) from sea anemone. *c*. Triple element, also from sea anemone, formed by addition of neuron (g). *d, e:* Schematized reflex arcs in earthworm and vertebrate. Receptor neuron (s) sends information from skin (i) into nerve cord (*d*) and spinal cord (*e*). Motoneuron (m) is excited, and its efferent impulse acts on muscle (ms; mf). (From 47).

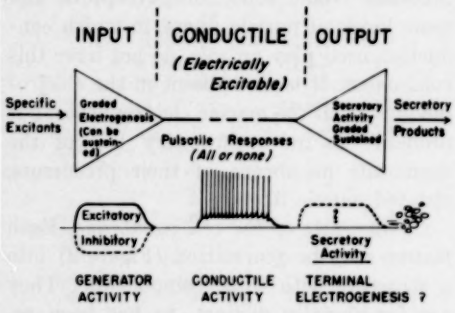


FIG. 2. Diagram of three responsive components of neuron. In actuality the different components (upper row) may be interspersed to various degrees. Electrogenic activity is on lower row, the thin line representing the resting potential. Hyperpolarizing, inhibitory activity is indicated by broken lines. The sustained, graded depolarizing generator (or synaptic) potential is represented as acting upon the conductile component to cause production of a train of spikes. The electrogenesis of the output, if it occurs, is as yet unknown. The effector membrane manifests its activity by release of a transmitter substance that can excite another synaptic membrane in a sequence of neurons. (From 40).

teraction in the functioning of the cell, and of their interplay in the cooperative activity of many cells in combination (42, 44, 46, 69, 70). Of all the organ systems of animals the neural mechanism is *par excellence* a cooperatively organized structure. Uniquely for this organ, the mere increase in the number of its cells tends to increase its functional complexities. These in turn permit increasingly elaborate relations between the animal and its environment (42, 47).

The detailed information already available on functional specifications of different membrane components poses a challenge to anatomy. Modern techniques of electrophysiology and pharmacology permit delineation of different portions in the membrane of a cell, by their widely different properties. These differences are not distinguishable even with the most refined techniques of modern microscopy. Nevertheless, electrophysiological and pharmacological data (45, 46, 49, 50, 76) indicate that these functional differences, in many cases at least, must be related to differences in chemical structure of the cell membrane.

ELECTROPHYSIOLOGICAL PROPERTIES

Differently excitable membranes. Fundamental in the new formulation was the recognition (1, 3, 35) that the excitable mem-

brane of the receptor (input) portion of the cell differs radically from the conductile membrane which generates spikes in a neuron or muscle fiber. The receptor membrane, while responding to one or to several types of specific excitants (chemical, mechanical, thermal, photic, etc.) does not respond to electrical stimuli. Thus, this component is *electrically inexcitable*, in contrast to the conductile membrane. The electrical excitability of the latter is its essential feature, which determines the capacity of this membrane to generate all-or-none impulses and thus to effect their decrementless propagation by means of local circuit excitation (*cf.* 58).

The potentials associated with activity of the input membrane are variously designated as receptor, generator, junction, endplate, and synaptic or postsynaptic potentials, depending on the tissue in which they have been observed. This variety stems in large measure from the wide range of specific excitants which initiate the individual responses and from the diversity of the forms which these responses may assume. The diversity, however, arises directly from the property common to all these systems, electrical inexcitability. Thus, the responses may be graded in amplitude and duration, depending upon the strength and duration of the stimulus. They may be of either depolarizing or hyperpolarizing sign, depending in the first place upon the nature of the electrogenic membrane and secondarily upon the electrochemical conditions under which the membrane performs its *transducer action* (37), the alteration of its permittivity to various ions. In sum, electrical inexcitability endows these responses with a constellation of properties which are distinctively different from those of electrically excitable membrane (Table 1), as will be described below.

Electrogenic processes. The electrogenic processes of the differently excitable membranes are also different (Figure 3). Basic to all are changes in ionic permittivity of

TABLE 1

Properties Which Distinguish Transmissional from Conductile Electrogenesis

A. *Conductile Response with Impulse (Spike)*	B. *Transmissional Responses (p.s.p.'s)*
1. Excited by depolarization, including electrical stimuli	Cell membrane not responsive to electrical stimuli
2. As above	Component of cell response not excited by electrical stimuli
3. Vanishingly brief latency	Long, irreducible latency
4. Always depolarizing, overshoot	Hyperpolarizing or depolarizing
5. All-or-none (except in special circumstances)	Graded, reversible in sign
6. Characteristic duration, never summated	Prolonged, sustained electrogenesis: *a*) to repetitive neural stimuli; *b*) to chemical excitants
7. Absolute and relative refractoriness	No refractoriness
8. Conduction at specific rate	Non-propagating ('standing') response
9. Blocked by hyperpolarization	Response during hyperpolarization
10. Inactivated by depolarization	Response during depolarization
11. Low sensitivity to drugs	Sensitive to pharmacological agents in two ways: *a*) synapse activation; *b*) synaptic blockade

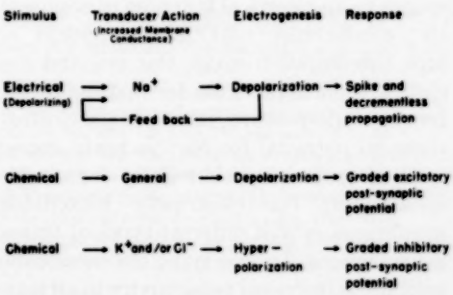


FIG. 3. The different types of electrogenesis. The electrically inexcitable components of this diagram are the chemically excitable depolarizing and hyperpolarizing synapses. The schema, however, also applies to receptors, the input membranes of which may be specifically responsive to other kinds of excitants. (From 38).

the excited membranes, but these transducer actions have kinetics that are characteristically different in time and degree, and involving different proportions of the three major inorganic ions, K^+, Na^+, and Cl^-.

(1) *Electrically excitable membrane.* An electrical stimulus, depolarization of the electrically excitable membrane in any manner (*e.g.* by an extrinsic applied current; a depolarizing p.s.p.; depolarization by ions) initiates increased Na^+ permeability (*cf.* 54), which leads to further depolarization, and more increase in Na^+ permeability. This regenerative process causes an explosive response, the shift of the membrane potential from a negative resting value, approximately at the electrochemical potential for K^+, to internal positivity which approximates the electrochemical potential of Na^+ in the system. It is believed (55) that other potential-determined (*i.e.* electrically excitable) processes, delayed enhanced K^+-conductance and Na^+-inactivation, determine the duration of the spike and others of its characteristics.

While the above is probably the ionic mechanism for spike electrogenesis in many and perhaps all animal cells, it is not the only one capable of producing depolarizing and overshooting electrically excitable responses. In the plant cell *Chara*, the response to an electrical stimulus is enhanced Cl^- conductance (30). Cl^- is present in high concentration inside this cell and the electrochemical potential for that ion therefore is inside-positive, just as is the electrochemical potential for Na^+ in squid axons.

(2) *Depolarizing electrically inexcitable membranes.* The electrically inexcitable membranes exhibit different types of transducer actions. In one type, the membrane response is increased permittivity to all ions, approximately simultaneously. This leads to a depolarizing electrogenesis, but one graded in proportion to the strength of the stimulus (chemical in case of synaptic membrane) and sustained as long as the stimulant is available (*cf.* Figures 5, 6, 8). At its maximum, the depolarization strikes an average between the levels of the K^+- and Cl^--potentials (inside negative) and the Na^+-potential (inside positive). This average is approximately at zero membrane polarization (*cf.* 13, 18, 24). Though the depolarization does not react upon the electrically inexcitable receptor membrane which generates it, it can stimulate and evoke spikes in electrically excitable membrane if that is present[4]. Hence arose the terms generator potential (33) and excitatory postsynaptic potentials or e.p.s.p.'s (18).

(3) *Hyperpolarizing electrically inexcitable membranes.* Three different kinds of transducer action appear to be capable of hyperpolarizing electrogenesis (Figure 3). Depending upon the ionic species involved—K^+, or Cl^-, or both (*cf.* 7, 18, 50, 60)—and the electrochemical conditions of the system, the transducer action may produce hyperpolarization, no marked change in resting potential, or even some depolarization. However, the activity of the membrane is always manifested by a tendency to resist any change from the "equilibrium" or "electrode" potential of the hyperpolarizing synapses. Thus, if depolarizing activity, excitatory for an electrically excitable membrane is generated at the same time, this depolarization is reduced or abolished. Its excitatory action is thereby diminished or inhibited, and the hyperpolarizing (or repolarizing) p.s.p.'s are therefore also designated as inhibitory or i.p.s.p.'s (18).

It should be noted, however, that depolarizing or hyperpolarizing potentials denote excitatory or inhibitory effects, respectively, only in the presence of electrically excitable membrane (39, 40, 46, 47). The tacit assumption that all cells have electrically excitable membrane gives rise to an incorrect invariant identification of these oppositely signed potentials with excitation

[4] This proviso is important as will be discussed below.

and inhibition (*e.g.* 34). Hyperpolarizing potentials occur in salivary gland cells which, though they do not produce spikes, are associated with secretory activity (63). Likewise, the hyperpolarizing potentials which occur in vertebrate retinal cells (51, 63, 67, 88, 90) may be satisfactorily incorporated (41, 43) into the general electrophysiological theory outlined in the present paper.

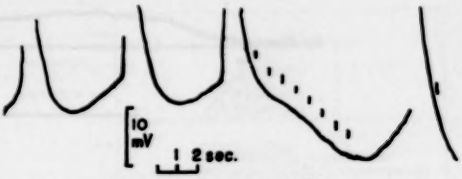


FIG. 4. Interaction of depolarizing and hyperpolarizing input electrogenesis with conductile activity. Microelectrode recording. Rhythmic depolarizations in sino-auricular node of frog are "pacemaker potentials" which lead to sudden onset of spikes. Only the bases of the latter are shown at the high amplification of the recording. After the third spike, a series of stimuli (marked by strokes) to the vagus nerve produced hyperpolarizing activity with suppression of the spikes. The spike produced after the train of stimuli stopped was followed by another vagal stimulus. (From 14).

Interaction of differently excitable components. Vertebrate cardiac muscle which, unlike the skeletal, possesses inhibitory synaptic activity, provides an example (Figure 4) of the interaction of depolarizing and

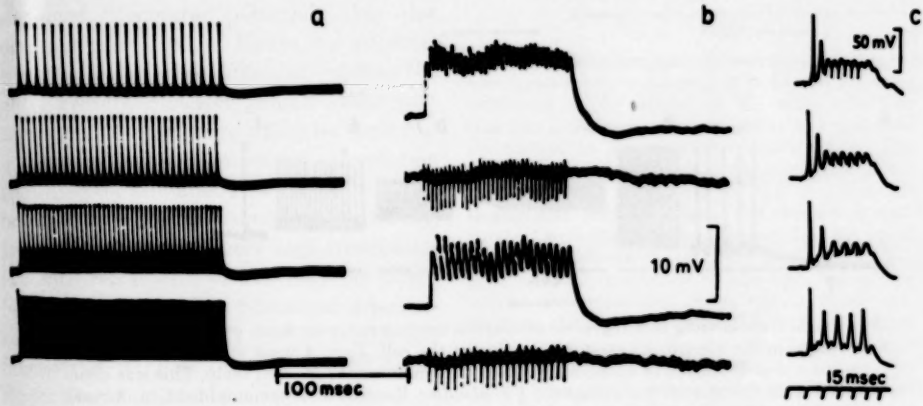


FIG. 5. Some consequences of the differently excitable electrogenic mechanisms in neurons. *a*. The cat motoneuron excited antidromically at high frequencies (140, 205, 280 and 630 per sec. ↓) produces pulsatile spikes, only their after-potentials fusing. *b*. The p.s.p.'s produced by orthodromic stimuli (205 and 280 per sec. ↑) summate, a higher average level of the depolarization being produced by the higher frequency of stimulation. The summated response is maintained as long as the afferent stimuli are delivered (lower record of each set). The amplitude calibration applies to the p.s.p.'s of this set which were taken at about 10× the amplification of *a*. *c*. Repetitive activity evoked in the rabbit cervical sympathetic neuron by stimulating the preganglionic supply at approximately 80, 100, 120 and 150 per sec. (↑). At the time scale of the records the first p.s.p. is not shown. The first stimulus evokes a large spike; but even at the lowest frequency, the spikes caused by the subsequent stimuli are small, while the p.s.p.'s are summed and sustained. This synaptic depolarization, increasing at higher frequencies of afferent drive, inactivates the spike-generating membrane. After the second, depressed spike its responses progressively decrease, and at the highest frequency disappear. The p.s.p.'s are generated as long as there is an influx of presynaptic stimuli. (From 46, after 18 and 21).

hyperpolarizing potentials with a spike generating component. Despite much study, the nature of the depolarizing "pacemaker" mechanism of the heart is still unknown. However, its effect is obvious, the production of a spike in the cardiac muscle when depolarization reaches a critical firing level for the electrically excitable membrane. On stimulating the vagus nerve the inhibitory synapses are activated, the depolarization

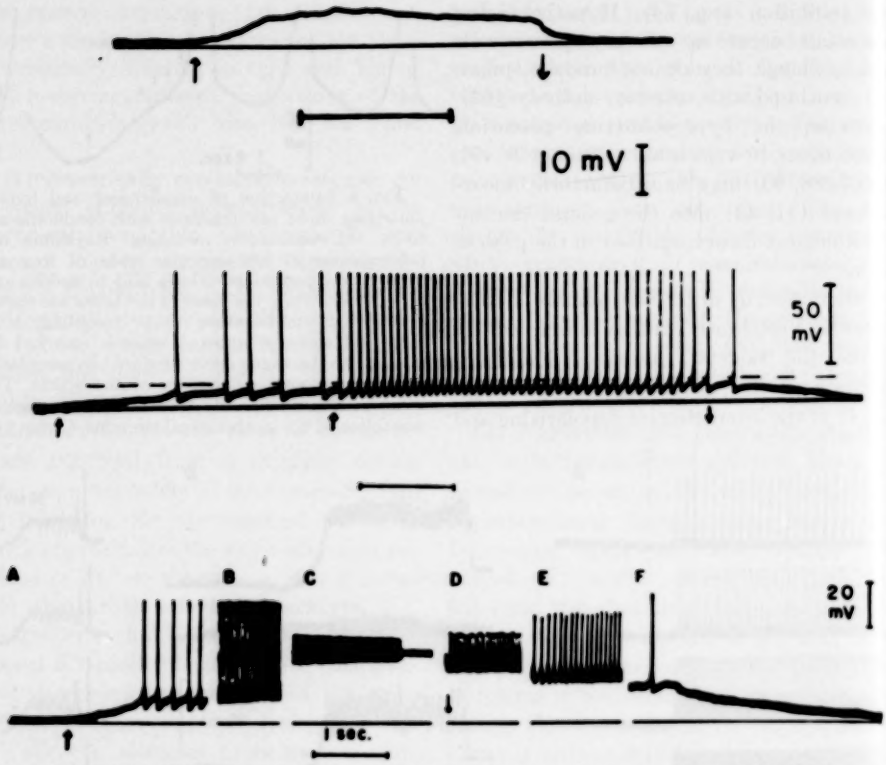


FIG. 6. Depolarizing electrogenesis of crayfish mechanoreceptor sense organ and the effects it evokes in the electrically excitable portion of the cell. *Top:* A weak stretch stimulus (↑) caused a depolarization of about 7 mv across the membrane of the cell body. This was maintained until the stretch was released (↓). *Middle:* Records at lower amplification. A weak stimulus produced a low frequency discharge of spikes. Increased stretch (second arrow) caused a higher frequency discharge which continued (with some slowing) as long as the stimulus was applied. *Bottom:* Three increasingly larger stimulations are shown in *A* to *C*. The spikes produced at high frequency by the strongest stimulus (*C*) were diminished in amplitude and at the end were no longer evoked, while the receptor continued to respond with its sustained, summated depolarization. *D* to *F:* The return of responsiveness of the electrically excitable membrane after its inactivation. Note that the average level of the depolarization produced by the mechanoreceptor dendrites is graded with the degree of the stimulus. (From 23).

is diminished or eliminated and spike production is slowed or stopped, leading to slowing or arrest of the heart-beat[5].

The interplay of different kinds of electrophysiological processes, involving transducer actions which obey different laws, leads to complications in overall behavior. One example is the effect known as Wedensky inhibition (Figure 5) which had previously not found a satisfactory explanation (37, 38). The effect stems from the capacity

[5] It is, of course, unnecessary to detail here the classical investigations of Otto Loewi (62), which provided the first direct evidence that vagal action of the heart was caused by a transmitter, identified with acetylcholine. The significance of Gaskell's demonstration (31) that the resting potential was increased on stimulating the vagus nerve was lost for many years (*cf.* 14) and the finding was even distorted to its opposite (*cf.* 28, p. 687). Monnier (66) suggested, before the discovery of the different varieties of synaptic potentials (6, 8, 19, 20, 26, 83), that inhibition might be caused by a process of intracellular hyperpolarization.

of p.s.p.'s to be summated (*b*)—unlike spikes (*a*)—in response to stimulation of the presynaptic nerve at high frequency. In various systems, the accumulation of depolarization from e.p.s.p.'s leads to more or less rapid inactivation of the spike-generating membrane. Therefore, at high frequencies of stimulation involving cells that are rapidly inactivated, the postsynaptic cell is capable of only a few spikes (*c*) before depolarizing blockade sets in.

An example of useful and deleterious interplays of the different kinds of membrane is provided by the behavior of the crayfish stretch receptor (Figure 6). A weak, long-lasting mechanical stimulus evokes a small sustained "generator potential," but this does not evoke spikes. Hence, no information about the weak stimulus reaches the nerve centers. Stronger stimuli evoke patterns of spike discharges which by their frequency and number do convey information regarding the stimulus. However, this coding breaks down when the stimulus is too strong. Impulses produced at very high frequencies fall into refractoriness and may no longer be propagated (1, 39). Sustained depolarization of the electrically excited membrane inactivates it. Thus, reports to the nerve center are again absent (Figure 7).

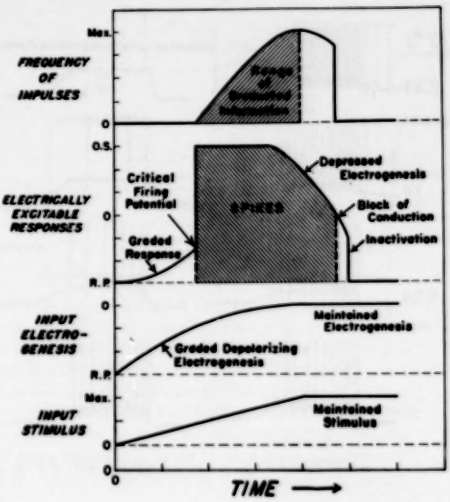


FIG. 7. Diagrammatic representation of the interrelation between stimulus at input and impulses conducted to the output of the same cell. The stimulus is increased linearly with time and then maintained at its maximal effective value. The depolarizing electrogenesis of the input reproduces the momentary amplitude of the stimulus, although with some distortion. The changes in electrically excitable responses caused by the input activity are shown in the next level of the diagram and the frequency of the impulses at the uppermost. Amplitudes of the spikes initially rising from the resting potential (R.P.) to overshoot (O.S.) approximately at the "sodium potential" decrease during continued activity at high frequency. Loss of all-or-none responsiveness followed by refractoriness and inactivation causes block of propagation and the end of spike production. Thus, the output receives no information within a range of weak stimulation of the input; then the information is roughly proportional to the stimulus, designated in the upper level as the range of graduated information; proportionality may be lost at the extreme upper range of information transmission. Finally, when propagation is lost, no information is transmitted. (From 47).

Other varieties of differences may be caused by the interactions of electrically inexcitable and excitable membrane (Figure 8). The photically generated potential of a *Limulus* photoreceptor and the spikes which are produced in the electrically excitable membrane of the same cell appear to undergo different modifications (29) in response to intracellular depolarization or hyperpolarization. These effects are easily accounted for as due to properties of differently excitable membrane. Indeed, such findings may be used with considerable assurance as experimental demonstrations of the presence of different membranes. For example (Figure 9), increase of a depolarizing p.s.p. during hyperpolarization of the cell, and inversion of a hyperpolarizing p.s.p. under the same conditions are directly deducible from their common property of electrical inexcitability (*cf.* Table 1).

The above examples serve to emphasize that the sign of the potential of electrically inexcitable membrane does not necessarily indicate the underlying processes which are determined by the nature of the electrogenic membrane. In cat motoneurons (Figure 10), apparently depolarizing responses

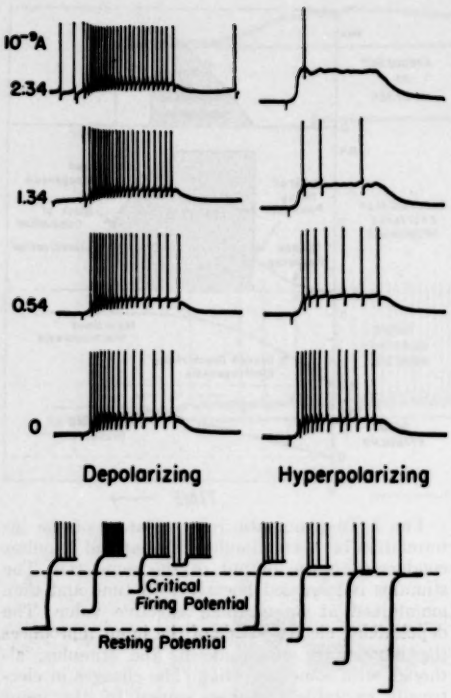


FIG. 8. Interaction of generator potential and polarizing voltages on electrically excitable membrane. Eccentric cell of *Limulus* eye was impaled with a microelectrode, used both for recording and for polarizing the cell. Magnitude of the applied currents are given on left. During polarization a constant light intensity was also delivered for about 1.5 sec. This stimulus gave rise to a depolarizing generator potential. The latter decreased with increasing depolarization (*left*) while the spike frequency increased. The strongest depolarization itself evoked spikes which recommenced after a silent period following the light stimulus. With increasing hyperpolarization of the cell (*right*) the generator potential increased, but the spike frequency decreased. The diagram indicates how these interactive effects occur. The smaller generator potential during depolarization was carried higher above the critical firing level. For the strongest hyperpolarizing current the generator potential barely attained the critical firing level. The changes in membrane potential from the resting level produced by the polarizing currents are drawn proportional to the applied currents, but the amplitude of the generator potential are exaggerated. (Modified from 29; full spike traces lost in original figure have been retouched. They were about 50 mv high and probably were generated not in the cell body, but in the axon.)

are produced in normally hyperpolarizing, inhibitory synaptic membrane, by increasing the membrane potential (I), or the intracellular Cl^- (II). In the first case the "depolarization" occurs only relatively to a hyperpolarized membrane (I), and does not become excitatory for the electrically excitable membrane. However, if the depolarization is absolute (*i.e.* it develops during the normal resting potential, II) the activity of the normally inhibitory synapse may produce spikes. Despite the variable sign of the potentials of both depolarizing and hyperpolarizing synapses, their membranes nevertheless retain pharmacological specificity (III). A "depolarizing" i.p.s.p. is eliminated by strychnine, while a similar e.p.s.p. is not affected (*cf.* 18).

Output membrane. To complete discussion of the physiological properties of the three components of neuronal membranes it would be desirable to characterize fully the properties of the effector portion. In its evolution this component is probably related to the various types of neurosecretory cells (38, 41). However, all too little is known as yet about this secretory element. Obviously, it responds to electrical impulses reaching it from the conductile component, and therefore it must itself be electrically excitable. Presumably, the secretory activity which is generated in response to a coded train of spikes is graded and may be sustained. When the phrenic nerve terminals to the diaphragm are depolarized (Figure 11) the frequency of "spontaneous" miniature e.p.s.p.'s of the muscle fibers is augmented (61). Hyperpolarization decreases the frequency. Excess Mg^+, which is presumed to depress the release of transmitter (*cf.* 13), abolishes the responsiveness to polarization, but does not eliminate the basal activity. This last finding suggests that the basal discharge of miniature e.p.p.'s is produced by a process akin to thermal agitation.

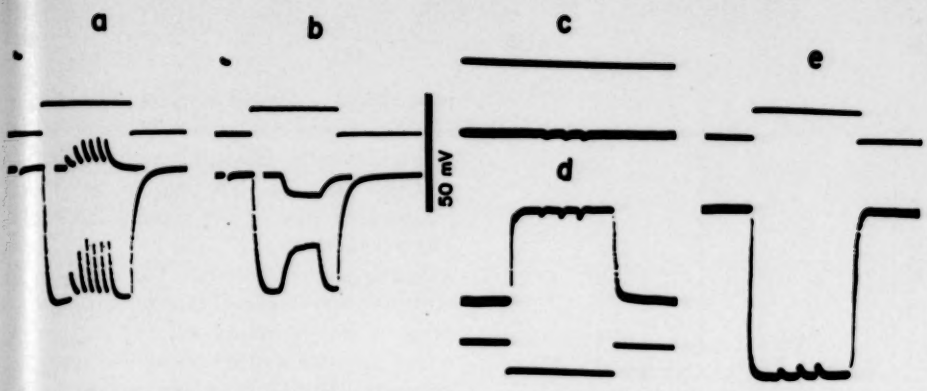


FIG. 9. Excitatory and inhibitory postsynaptic potentials recorded in a lobster muscle fiber. *a*. The e.p.s.p.'s to stimulation of the excitatory axon at 10/sec; at the resting membrane potential (inset) and on hyperpolarizing the membrane with a current (recorded as an upward deflection on the upper trace) through another intracellular electrode. The current pulse lasted 1 sec. Amplifier calibration (50 mv) is shown by the 100 msec pulse at the beginning of the voltage trace. *b*. The response under the same conditions to stimulating the inhibitory axon of the same muscle fibers at 100/sec. *c, d, e:* Another muscle fiber, responding to stimulation of the inhibitory axon at 5/sec. The i.p.s.p.'s (*c*) were unusually large in this fiber. They were augmented by depolarization (*d*) and inverted by hyperpolarization (*e*). The absolute value of the resting potential is not shown. (From 50).

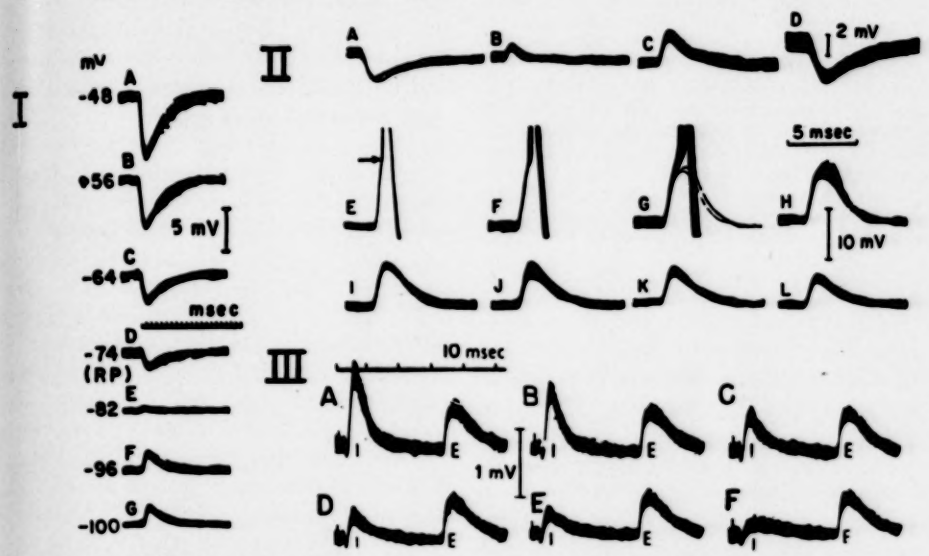


FIG. 10. Changes produced in i.p.s.p.'s of biceps-semitendinosus motoneurons of cat by polarizing (I); by changing ionic composition (II); and by strychnine (III). I. Depolarizing the cell (*A–C*) from the resting potential (*D*) increased the hyperpolarizing p.s.p. Hyperpolarization of the cell (*E–G*) decreased and inverted the p.s.p. II. The p.s.p. (*A*) was inverted (*B, C*) "spontaneously," probably by diffusion of KCl from the microelectrode. The sign of the p.s.p. was again changed by depolarizing the cell to −27 mv. *E–L:* Sequence of recordings after the ionic composition had been drastically changed (increased Cl^-, decreased K^+), but the resting potential was not significantly affected. The large inverted, depolarizing i.p.s.p. was now excitatory, producing a spike (*E*). As the Cl^- leaked out the depolarization diminished, the spike appearing later (*F, G*) and then being eliminated (*G–L*). III. Prior to this series of records the i.p.s.p. was inverted by diffusing Cl^- into the cell. This depolarizing response is shown (marked I) at the beginning of each trace (*A–F*). Following it is an e.p.s.p. (marked *E*) produced by stimulating excitatory afferents to the motoneurons. Strychnine salicylate (0.1 mg/kg) was injected after *A*, causing progressive diminution of i.p.s.p. but not of e.p.s.p. during the next 4 ten-sec intervals (*B–E*). The i.p.s.p. almost disappeared (*F*) upon a second injection of strychnine. (From 46, after 18).

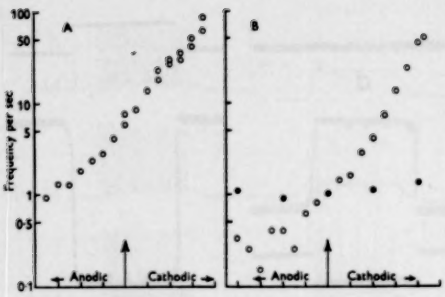


FIG. 11. Effects upon the frequency of miniature e.p.p.'s in rat diaphragm muscle fibers of electrotonus applied to the phrenic nerve. Abscissae show the intensity of applied electrotonic current in relative units; ordinates, the frequency of miniature e.p.p.'s scaled logarithmically. Arrows point to frequencies of the latter observed when no electrotonic currents were applied. "Cathode" current is depolarizing for the nerve terminals, "anodic" is hyperpolarizing. *A*. The effects of the change in potential were essentially symmetrical on the logarithmic scale, increased frequency of miniature e.p.p.'s with cathodic and decreased frequency with anodic current. This was the most frequently encountered result. *B, open circles*. Terminal depolarization was much more effective than hyperpolarization in changing the frequency in this experiment; *filled circles*, the same muscle was exposed to 12 mmole magnesium (normal concentration is 1 mmole). The frequency of miniature e.p.p.'s became essentially independent of the membrane potential of the nerve fibers. (From 61).

PHARMACOLOGICAL PROPERTIES

Chemical vs. electrical transmission. Electrical inexcitability of synaptic membrane rules out the electrical theory of transmission which was proposed in the 1860's (*cf.* 36). The only alternative theory available at present is that of chemical transmission. Sensitivity of the synaptic membrane to chemical transmitter agents probably is also responsible for the high sensitivity of synapses to many other chemicals, or synaptic drugs. In contrast, the electrically excitable membrane is relatively insensitive to most drugs[6]. Consideration of the nature of pharmacological actions in terms of the concepts outlined above has permitted analysis of pharmacological effects, not only in simple systems (38, 45), but also in the more complicated case of the mammalian brain (40, 44–46, 69–81).

Synapse activator drugs. The frog neuromuscular preparation illustrates various aspects of the excitatory action of a transmitter agent on a relatively simple synaptic structure (59). A brief electrophoretically applied jet of acetylcholine was an adequate stimulus to the endplate, (Figure 12), causing a brief depolarization. Longer-lasting jets produced longer-lasting potentials, which were larger when the chemical stimulus (*synapse activator*) was stronger. These same stimuli continued to evoke the synaptic responses when the electrically excitable component of the muscle fiber was inactivated because the fiber was exposed to isotonic K_2SO_4 and was also polarized internally positive by an applied current. Under these electrochemical conditions the depolarizing p.s.p. was inverted in sign. Thus, the electrically inexcitable membrane responded to a chemical agent in exactly the way that was expected (Table 1). A complicating factor, "desensitization" (*cf.* 59), or loss of responsiveness to sustained application of the drug (38, 39) is also illustrated in the experiment, but need not be considered further.

Synapse inactivator drugs. The eel electroplaque furnishes another simple system in which pharmacological data are clearly presented. Procaine (Figure 13), like eserine, d-tubocurarine and other *synapse inactivators*, blocks the development of the e.p.s.p. in response to neural stimuli. These

[6] Electrically excitable membrane is extremely sensitive, however, to the veratrum alkaloids and related compounds (*cf.* 84). The electrically excitable membrane of eel electroplaques is affected, though much more slowly than is the synaptic component, by substances like d-tubocurarine, eserine, etc., which block synaptic activity. This suggests that at least in some types of excitable cells the electrically excitable membrane may be related in chemical structure to synaptic membrane. An interesting finding in line with this view is the effect of denervation of muscle fibers upon their sensitivity to acetylcholine (4). Whereas the innervated fiber is particularly sensitive to the drug only at the endplate, other parts of the muscle fiber membrane also become very sensitive upon denervation.

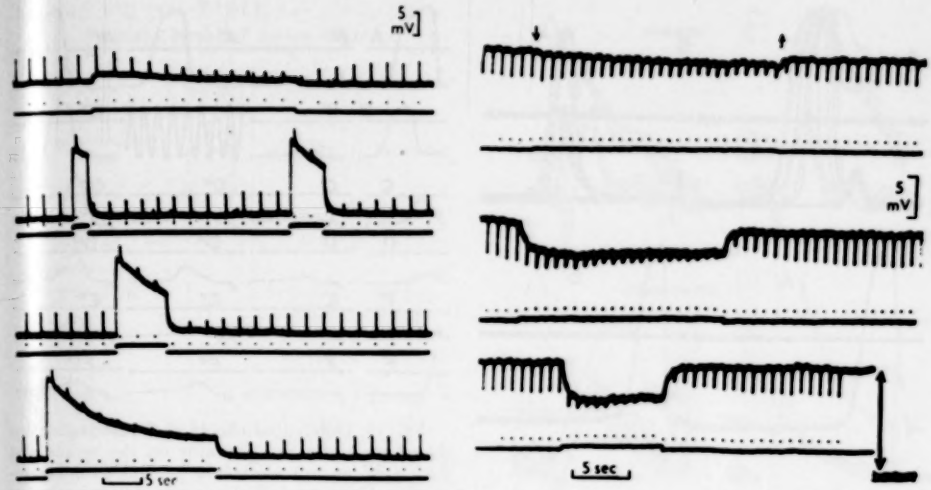


FIG. 12. Distinctive electrophysiological and pharmacological properties of electrically inexcitable synaptic membrane. Intracellular recordings at endplate of frog skeletal muscle fiber of responses to brief jets of acetylcholine and to longer applications of the drug. *Left*. The latter produce longer lasting depolarizations that are initially large, but diminish in time. The testing responses to the brief jets also diminish at the same time, indicating that sustained application of acetylcholine decreases the sensitivity of the receptive membrane to the drug. *Right*. The preparation was placed in isotonic K_2SO_4 which depolarized the tested muscle fiber. Intracellularly applied current polarized the muscle fiber to about 15 mv inside positive. Under the changed electrochemical condition the synaptic responses evoked by the drug appeared as an electrogenesis of reversed sign, but the properties of the activity were essentially unchanged. In the lowest trace the arrow indicates that the muscle fiber had been polarized inside-positive by about 15 mv. (From 59).

drugs do not themselves depolarize the cell, and they antagonize the depolarizing action of the synapse activator drugs. The cell remains directly excitable for a long time after neural excitability is blocked.

Depolarizing blockade. In contrast is the complicating effect of blockade by the synapse activator drugs, such as acetylcholine, carbamylcholine or decamethonium (Figure 14). The sustained depolarization which is caused by the activity of the excitatory synapses inactivates the electrically excitable membrane. Neural stimuli therefore may continue to evoke e.p.s.p.'s, but the latter no longer have a functional electrically excitable membrane to operate upon. In contrast to the curarization shown in Figure 13, depolarizing blockade, which is related to Wedensky inhibition (Figure 5) and to blockade by "overstimulation" (Figure 6) renders the electrically excitable membrane unresponsive to direct stimuli.

Complex synaptic systems. In more complexly organized synaptic systems, hyperpolarizing, inhibitory as well as depolarizing, excitatory synapses may be acted upon by the drugs. Accordingly, the effects of these actions may become complicated. The occurrence of two major varieties of synaptic drugs (activators and inactivators) and of two major varieties of synapses (excitatory and inhibitory) can give rise to six varieties of action, depending on whether the drugs affect one or both synaptic varieties (Table 2). However, the overt effects are in general only of two kinds, "excitation" or "inhibition." The same overt effect thus can be produced by drugs of entirely different fundamental action. For example, strychnine and Metrazol are both classified

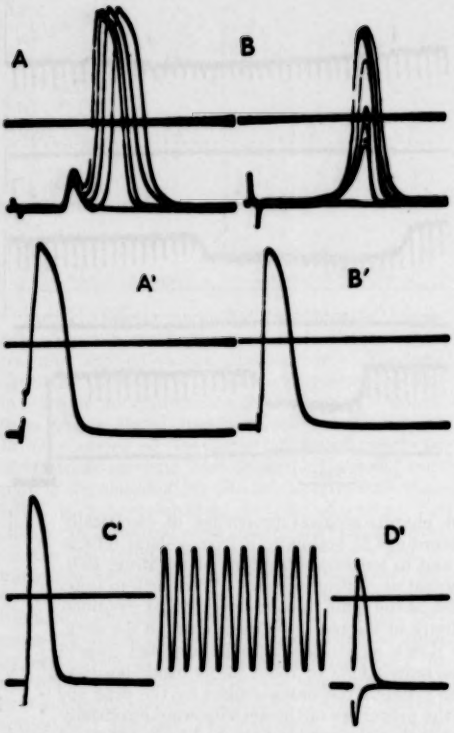


FIG. 13. The mode of action of a synapse inactivator drug. Eel electroplaque, intracellular recording. *A*. A single volley to the nerve evoked only a p.s.p., spikes being produced by facilitation during repetitive stimulation at 10/sec. *A''*, the directly evoked spike. *B*. 10 min after exposure of the cell to procaine (1 mg/ml) facilitation by repetitive neural stimulation at 50/sec became ineffective for eliciting a p.s.p. and transmissional blockade ensued. The cell continued to be directly excitable at this time (*B'*) and 17 min later (*C'*), although the response was probably modified into graded activity. Eventually the electrically excitable membrane also became unresponsive to very strong stimuli (*D'*, after 115 min), reflecting the anesthetic action of procaine. The resting potential of the cell was not affected by the synapse inactivator drug, which also prevented a depolarizing action by 10 μg/ml carbamylcholine, added 74 min before the last record was taken. Calibration 100 mv and msec. (From 2).

as stimulants of the central nervous system (17, 32) on the basis of their common overt convulsant action in the nervous system. However, they produce these overt effects by different mechanisms (Table 2).

Differential analysis of overtly similar

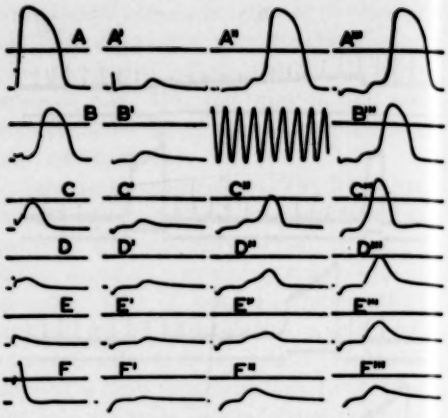


FIG. 14. Differential effects of depolarization induced by a synapse activator on the spikes and p.s.p.'s of an eel electroplaque. Intracellular recording. Columns *A–F*, direct stimulation; columns *A'–F'*, etc., weak, moderately strong, and very strong stimuli to the nerve. *A–A'''*, the response of the normal cell. The strong direct stimulus evoked a spike with very brief latency (*A*). The weak neural volley caused a p.s.p. (*A'*), the stronger also a spike (*A''*, *A'''*). The cell was then treated with weak eserine solution (25 μg/ml) for 78 min, and weak acetylcholine (1 μg/ml) for the last 58 min. of that period. These drugs had no effect on the potentials. Five μg/ml acetylcholine were then added. Depolarization developed, the spikes 36 min later becoming smaller, but the p.s.p. was unaffected (*B'–B''*). The diminishing electrically evoked response 9 min later (*C–C'''*) became graded, as seen by its larger size in response to the stronger neural volley. These effects progressed during the next 19 min (*D–D'''*) and 11 min thereafter (*E–E'''*). The p.s.p. to the threshold neural volley decreased (*E'*), but was still evident (*F'*) when the electrically excitable membrane no longer responded to a much stronger direct stimulus (*F*). The p.s.p., to a maximal neural stimulation (*F'''*), was still about as large as initially (*A'''*). This p.s.p. was still capable of evoking a small graded response of the electrically excitable membrane, as seen by the small delayed additional potential on the falling phase. Note that desensitization by acetylcholine is small or absent in this preparation. (From 2).

actions. An illustration of this is the differential action of the two drugs on two cortical systems, the cerebral and cerebellar (80)[7]. Topically applied strychnine in-

[7] The following discussion of cortical potentials and of their pharmacology is based on the view that the potentials recorded from the cortical surfaces, and in special cases also from various deep structures, are chiefly—often exclusively—com-

TABLE 2
Synaptic Modes of Action of Drugs

Type of Synaptic Drug	Type of Synapse		Type Compounds	Type Effect
	Depolarizing	Hyperpolarizing		
Activators				
Non-selective	+	+	Acetylcholine Norepinephrine	Excitatory or Inhibitory
Selective (a)	+	0	Metrazol Picrotoxin	Excitatory
(b)	0	+	?	Inhibitory
Inactivators				
Non-selective	+	+	d-Tubocurarine	Inhibitory
Selective (a)	+	0	GABA,	Inhibitory
(b)	0	+	Strychnine	Excitatory

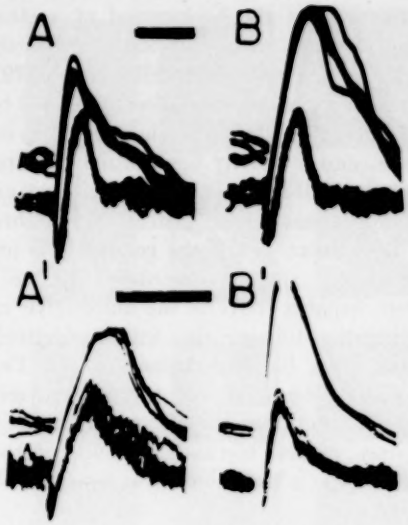


FIG. 15. Different effects of drugs upon different synaptic substrates. Two preparations, that of *A'*, *B'* heavily heparinized (50 mg/kg i.v.). *A*, *A'*. Simultaneously recorded cerebral (upper trace) and cerebellar (lower trace) SCR's. *B*. Cerebral response was augmented while cerebellar was not affected by topical applications of strychnine (0.1 per cent). *B'*. Similar results were obtained by injecting d-tubocurarine (2 mg/kg) into the heparinized preparation. Explanation in text. In this and all subsequent figures on cortical potentials, negativity at the active recording lead is denoted by an upward deflection. A number of traces of successive responses are superimposed in each record to show the small degree of variation during the experiments. Time calibrations 20 msec. (*A*, *B*, unpublished experiments by Purpura and Grundfest; *A'*, *B'*, from 80).

creases markedly the amplitude of the superficial cortical response (SCR) of the cat cerebral cortex (Figure 15), but on the cerebellar cortex it is relatively inert. Metrazol, on the other hand, produces spiking when topically applied to the cerebellar as well as to the cerebral cortex, and its effects may also be clearly distinguished in other ways (*cf.* 80, Figure 14). This difference in the actions of the two "stimulant" drugs lies in the difference in synaptic substrate offered by the two cortical structures. The cerebral SCR has an appreciable component of surface-positive, axodendritic synaptic activity which is masked by a larger surface-negative component (79). By eliminating the surface-positive component, which is presumed to be due to hyperpolarizing inhibitory p.s.p.'s (*cf.* Figure 10), the full magnitude of the surface-negative, depolarizing, excitatory p.s.p.'s is disclosed. In the cerebellar SCR, however, the surface-positive component of hyperpolarizing, inhibitory p.s.p.'s is either small or absent (80). Strychnine therefore has no synaptic substrate to act upon and the cerebellar SCR is unaffected by this drug. Metrazol, on the other hand, activates excitatory synapses, which are present in both cortical structures. In both, therefore, topically applied Metrazol causes convulsant activity.

Figure 15 also illustrates how a change in action may be produced when a drug op-

posed of mixtures, in various proportions, of excitatory and inhibitory p.s.p.'s. In the surface potentials of the cerebral and cerebellar cortex these are largely due to the activity of the dendritic arborizations of the superficial cortical layers and therefore are chiefly axodendritic p.s.p.'s. The evidence for these conclusions is presented and discussed in references 38, 40, 42, 44–46, 69–81, and 85.

erates against the background of another drug. Heparin does not itself affect the SCR's of cerebral or cerebellar cortex (79). However, it modifies the effects produced by d-tubocurarine. When the latter drug is injected into a heavily heparinized preparation, the SCR's are not abolished as they are in unheparinized cats. Instead, the cerebral SCR augments while the cerebellar is unaffected or slightly diminished (*A'*, *B'*). Thus, heparin converts the unselective inactivator, d-tubocurarine, into a selectively acting drug like strychnine (*A*, *B*). This probably occurs by the protection which heparin affords to the excitatory synapses against curare blockade. d-Tubocurarine then acts as a "selective" drug because only the inhibitory synapses are still susceptible to inactivation. It should be noted further that strychnine itself is not a highly selective drug. In higher concentrations it is a general synapse inactivator (80) and this is its primary effect in new-born mice in which inhibitory activity apparently is not yet developed (76). In topical applications of the 0.1 per cent solution, as in Figure 15*B*, the initial cerebral effect is followed by later depression of both SCR's.

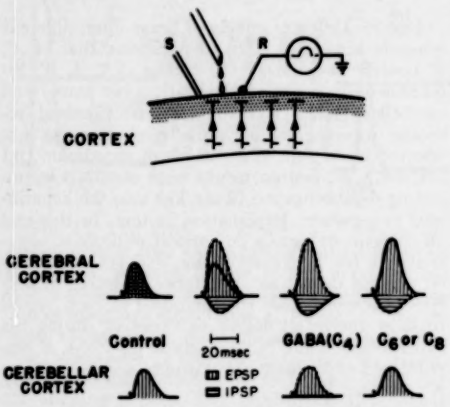


FIG. 16. Effects of topical applications of selectively inactivating drugs on cerebral and cerebellar cortical responses. *Above:* Diagram of experimental arrangement indicating surface stimulating electrodes (S) and recording (R). The drug is applied with a syringe. Apical dendrites emphasized in the diagrammatic representation of cortico-spinal neurons. *Below:* Schematized surface-negative SCR's. That of cerebral cortex is shown in second diagram (solid line) as composed of mixture of depolarizing (surface-negative) and hyperpolarizing (surface-positive) p.s.p.'s each drawn in broken lines. The cerebellar SCR is represented as purely a depolarizing e.p.s.p. Application of GABA to cortical surfaces eliminates the e.p.s.p.'s in both SCR's, the inversion of the response in the cerebral cortex (solid line) disclosing the otherwise masked i.p.s.p. Strychnine, or longer-chain ω-amino acids (C_6 or C_8) eliminate selectively the i.p.s.p.'s, the cerebral SCR thus increasing (solid line) while the cerebellar SCR is unaffected.

Amino acid drugs. New data obtained with a newly-discovered series of drugs, the ω-amino acids and related compounds (71, 73, 76), confirm and extend the conclusions described above. The employment of these substances as experimental tools is particularly advantageous because of three factors. 1) Topically applied to the cortex they act with great rapidity and are reversible. 2) Their effects are restricted to the axodendritic synapses, and 3) depending upon their chemical structure, and notably on carbon-chain length, these drugs inactivate selectively either the depolarizing, excitatory axodendritic synapses, or the hyperpolarizing, inhibitory.

On the SCR's of the cerebral and cerebellar cortices, therefore, the two types of drugs should exert quite different actions (Figure 16). Elimination of the excitatory p.s.p.'s from the cerebral cortex should change the surface-negativity to a positivity which discloses the remaining hyperpolarizing, inhibitory p.s.p.'s. The cerebellar SCR, on the other hand, should be abolished, since there would be little or no contribution of hidden inhibitory p.s.p.'s. Substances which selectively eliminate the hyperpolarizing, inhibitory p.s.p.'s should act like strychnine (Figure 15). The cerebral SCR should increase, while the cerebellar should remain unaffected. These substances also should produce convulsant activity in the cerebral cortex, but not in the cerebellar. All these expectations have proved correct.

The short-chain ω-amino acids, ranging

from glycine (C_2) through δ-amino valeric acid (C_5) all invert the cerebral SCR (Figure 17) and eliminate the cerebellar. The most powerfully acting substances are β-alanine (C_3), γ-aminobutyric acid (C_4 or GABA) and β-OH GABA (76). The longer-chain ω-amino acids all act like strychnine, and are convulsant agents. They augment the cerebral SCR (Figure 18), but do not affect the cerebellar response.

Role of naturally occurring amino acid drugs. Other compounds with structures related to the ω-amino acids are also synaptic drugs (Table 3)[8]. Of considerable interest is the fact that a number of commonly occurring substances, such as creatine and creatinine (Figure 18) and some vitamins belong in this group. Thus, these substances, in addition to their roles in metabolism, may have synaptic actions in the normally functioning organism (48). Indeed, attention has recently focussed on the fact that a number of these agents occur naturally in the brain (Table 4), some in relatively high concentration. If they do act as synaptic drugs these substances would have to be classified as a new variety of "transmitter" (44–46, 76) whose function as inactivators would be to diminish p.s.p.'s evoked by other agents, transmitters that are activators.

Analytical employment of amino acid drugs. The availability of these synaptic agents, the numerous possibilities for modifying their structures, and the availability of means for analyzing their actions, as well as a number of other properties (76) have provided a new series of tools for the study of various aspects of synaptic pharmacology and physiology.

(1) *Identification of modes of action of drugs.* They provide a new means for analyzing fundamental actions of different drugs. Thus, the different kinds of interaction of GABA with picrotoxin and strychnine (Figure 19) demonstrate the different modes of action of these two "stimulants of the nervous system." Strychnine, as an in-

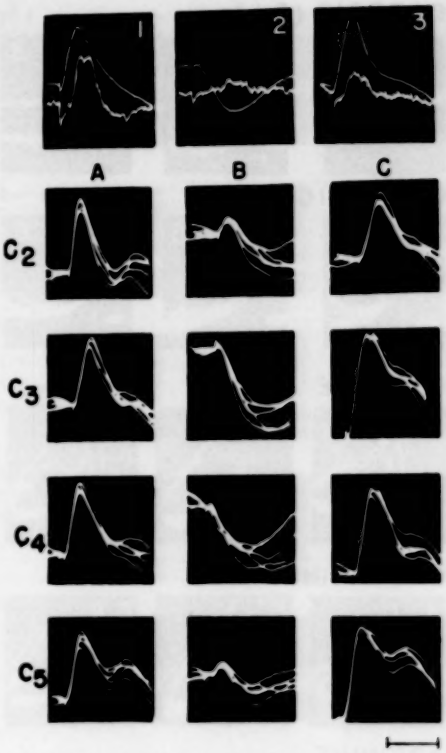


FIG. 17. Actions of ω-amino acids that are selective blockaders of depolarizing (excitatory) dendritic synapses. *Above.* Simultaneous recordings from cerebral (upper trace) and cerebellar cortex. The surface negative response of the cerebellum (lower trace 1) is eliminated (2) on topical application of GABA (5 drops 0.1 per cent solution). That of the cerebral cortex is converted to positivity. 3, two min after flushing the cortical surfaces with Ringer's solution. *Below.* The comparative actions on cerebral cortex of four ω-amino acids of carbon chain lengths C = 2 to C = 5. *Column A:* Surface negative responses before applying the drugs, were reversed to positivity (*B*), but to different degrees 2 min after topical application of 0.2 c.c. of the amino acids in 1 per cent solution. *C.* 5 min after flushing the cortex with Ringer's solution. Five superimposed traces in each record, all the tests having been done on the same preparation. (From 44, after 76).

[8] Recent work (unpublished) has expanded the range of substitutions that can be made in the ω-amino acids and still retain synaptic actions. Thus, the chain —N— of guanidino acids may be replaced by —S— to form synaptically active *iso*-thioureido acids. The double bonded γ-amino-crotonic acid acts like GABA.

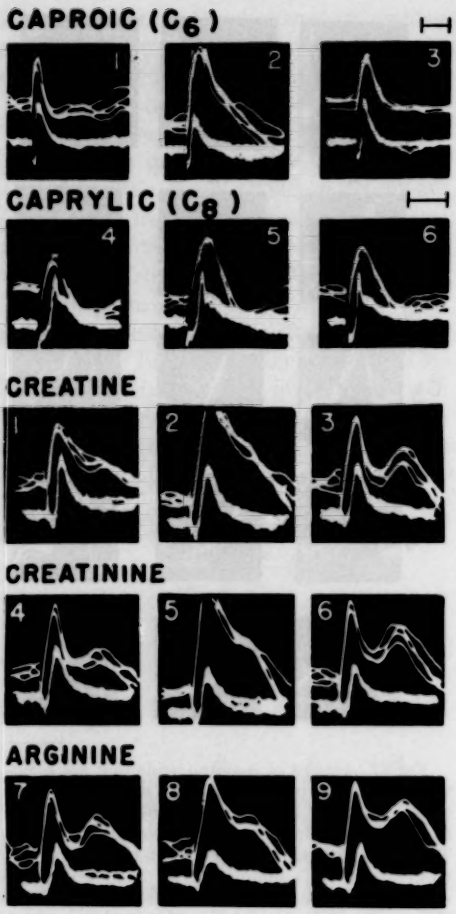


FIG. 18. Actions of selective blockaders of hyperpolarizing, inhibitory dendritic synapses. Each row represents the test of a different amino acid. *Left column:* The cerebral (upper trace) and cerebellar response before application of a compound. *Middle column:* 1 min after applying the synaptic agents to the two recording sites. *Right column:* 20 min after rinsing the cortical surface with Ringer's solution. From above down: ε-amino caproic acid (C_6); ω-amino caprylic acid (C_8); Creatine (methyl guanidino acetic acid); Creatinine (the condensed form); Arginine (derived from δ-guanidino valeric acid). All but the latter substance augment strongly the cerebral dendritic response, but affect the cerebellar little or not at all. δ-Guanidino valeric acid is a powerful blockader of inhibitory synapses. Insertion of the α-amino group created the weakly acting arginine. Time lines 20 msec. (From 44, after 76).

activator of inhibitory synapses (Table 2) complements GABA, which inactivates the excitatory. Application of both drugs to the cerebral cortex therefore eliminates both components of the SCR. On the other hand, picrotoxin antagonizes the action of GABA, confirming that like Metrazol it is an activator of excitatory synapses, and therefore a competitive antagonist of GABA (45).

(2) *Determination of different varieties of synapses.* As noted above, these compounds have demonstrated pharmacological differences between axodendritic and axosomatic synapses, differences hitherto clearly known only in anatomical terms (12). They do not affect synapses of skeletal muscle or of several types of receptor membrane (85). It is likely, however, that several varieties of autonomic synapses are affected (*cf.* 76; 27, 53). Thus, new pharmacological distinction can now be made amongst different kinds of electrically inexcitable membranes.

(3) *Studies on the blood-brain barrier.* The amino acid drugs do not penetrate the blood-brain barrier. Accordingly, when injected systemically they do not affect the cortical responses significantly (76). However, the barrier may be damaged or destroyed in localized cortical regions (76–78). In these regions, and only in these, the systemic injection of small quantities of the drugs produces results identical with those of topical applications to the cortex itself. Thus, the technique offers possibilities for studying, by electrophysiological and pharmacological means, the baffling problems of the blood-brain barrier[9].

(4) *Analysis of synaptic organization.* The selectively acting amino acid drugs have recently been used extensively to analyze the synaptic composition of various

[9] Various vasomotor and other autonomic effects produced by systemic injections of GABA and related compounds (*cf.* 76) apparently are produced by the action of the drug on the brain stem (86). The blood-brain barrier is presumed to be absent in part of this region.

TABLE 3

Cortical Synaptic Actions of Aliphatic Amino and Guanidino Acids

n = / Acids: R = CH_2 and CH_3	2	3	4	5	6	8	9
α-amino R_{n-2}—CH(—NH_2)—COOH	glycine	0 alanine	0 α-amino butyric	0 norvaline	0 norleucine		
ω-amino NH_2—R_{n-1}—COOH	−−	−−−− β-alanine	−−−− γ-amino butyric	−− δ-amino valeric	+++ ε-amino caproic	++++ ω-amino caprylic	++++ ω-amino nonanoic
α-ω-diamino NH_2—R_{n-2}—CH(—NH_2)—COOH			− 2,4-diamino butyric	0 ornithine	+ lysine		
ω-guanidino NH_2—C(=NH)—N(H)—R_{n-1}—COOH	−−−− guanidino acetic	−−−− β-guanidino propionic	++++ γ-guanidino butyric	++++ δ-guanidino valeric			++++ ω-guanidino nonanoic
α-guanidino R_{n-2}—C(—NH—C(=NH)—NH_2)—COOH		++ α-guanidino propionic	++ α-guanidino butyric				

Symbols: − to −−−−, increasing blockade of excitatory synapses and overt 'inhibitory' action on cerebral cortex. + to ++++, increasing blockade of inhibitory synapses and overt 'excitatory' action on cerebral cortex. Some of the guanidino compounds have actions of both types. 0, compounds not active: ω-guanidino acids act like n + 2 ω-amino acids.

cortical activities (44, 69, 74, 75, 81). For instance, some responses of the paramedian lobule of the cerebellum are affected by strychnine, whereas others are not (56, 74). Examples of both are seen in Figure 20, which also shows how the differences may be analyzed with the use of two selectively acting amino acid drugs, GABA (C_4) and ε-amino caproic acid (C_6). The SCR of the paramedian lobule, like the SCR in other regions of cerebellar cortex (Figure 17) was eliminated by a topical application of GABA. It was not affected by C_6 or by strychnine, indicating that as in other cerebellar regions (*cf.* Figures 15, 18) this response lacked an appreciable component of hyperpolarizing inhibitory axodendritic synapses. On the other hand, the response evoked in the same cortical region by stimu-

TABLE 4

Some Synaptically Active Amino Acids or Derivatives Found in Brain

Inactivators of:	Substances
A. Depolarizing axodendritic synapses	Glycine
	β-Alanine
	γ-Amino butyric acid
	γ-Amino β-OH butyric acid
	Guanidino acetic acid
B. Hyperpolarizing axodendritic synapses	Creatine
	Creatinine
	γ-Guanidino butyric acid

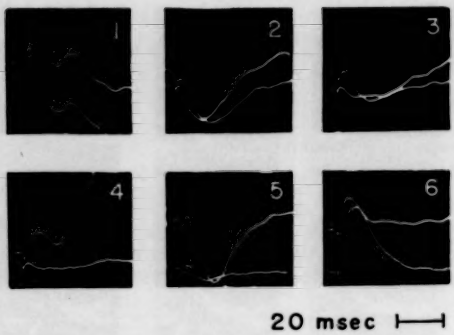


FIG. 19. Differential interactions of GABA with strychnine and picrotoxin. Simultaneous recordings of SCR's evoked independently in homologous sites of right (*upper trace*) and left (*lower trace*) anterior suprasylvian gyrus. Callosal section had disconnected the cerebral hemispheres. *1, 2:* Before and after applying GABA to each site. *3, 4:* Picrotoxin and strychnine were applied to right and left cortical sites respectively. Strychnine eliminated the surface-positive response, while picrotoxin diminished and eventually inverted the potential, also causing convulsive discharge. *5:* Application of more GABA counteracted both effects, that of strychnine somewhat less. *6:* Reversal of all drug actions after washing cortical surface with Ringer's solution. Note the augmented SCR of left cortex, which indicates that strychnine was still blocking some of the inhibitory synapses, as in Fig. 15. (From 76).

lating the contralateral cerebral cortex (Figure 20) was affected differentially by the two amino acid drugs. Like strychnine, C_6 eliminated the second of the two surface positive components, and brought out a later negativity. GABA, however, augmented and prolonged this second positive component. Since the substances act selectively, it is possible to deduce the synaptic components from the algebraic addition of the potentials. Thus, it is seen that two different pathways of activating cortical synapses evoke differently constituted complexes of synaptic events. Indeed, still other ways of exciting the paramedian cerebellar cortex evoke activities with entirely different pharmacological properties (74).

COMPARATIVE ELECTROPHYSIOLOGY AND PHARMACOLOGY

Comparative electrophysiology. The remarkably good concordance between elec-

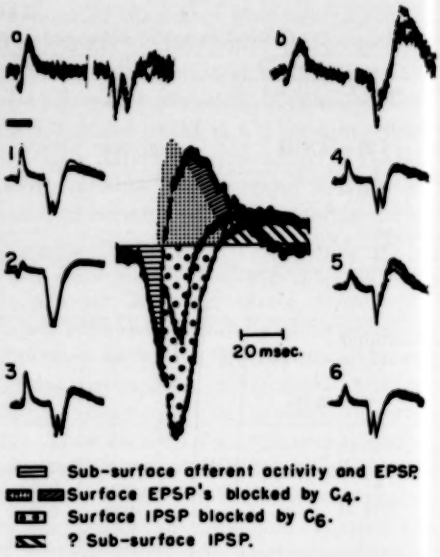


FIG. 20. Analysis of different pharmacological effects on different responses in one cortical region. Paramedian lobule of cerebellum: *a, b,* effects of topically applied strychnine (0.1 per cent solution). *1–3,* effects of GABA; *4–6,* of C_6, both applied in 1 per cent solution. Two cortical responses are shown in each record. First is a predominantly surface-negative SCR evoked by stimulating the paramedian lobule. Next is a cerebro-cerebellar response produced by stimulating the contralateral pericruciate cerebral cortex. This activity is composed of two surface-positive elevations (*a, 1, 4*). Strychnine (*b*) and C_6 (*5*) did not affect the SCR, but eliminated the second positivity of the cerebro-cerebellar response and brought out a large surface-negative potential. GABA eliminated the SCR (*2*) leaving behind a small diphasic component of action potentials. The cerebro-cerebellar response was augmented by growth of its second positive component. Reversibility of these effects is shown in *3* and *6* about 15 min. after washing out the amino acids. The SCR of the paramedian lobule is thus shown to be composed chiefly of surface-negative axodendritic e.p.s.p.'s. Analysis of the cerebro-cerebellar response is shown in central inset, in which records *2, 4* and *5* are superimposed. An early positivity and perhaps a late small negativity represent subsurface activity which is not affected by the amino acid drugs. A large component of surface-positivity ascribed to axodendritic i.p.s.p.'s (large dots) is characteristic of the paramedian lobule and is disclosed by application of GABA. Blockade by C_6 reveals a smaller, normally obscured surface-negativity (small dots) and an additional component of axodendritic e.p.s.p.'s (closely spaced diagonals) elicited by the stimulus in the absence of the i.p.s.p.'s. The time scale in upper left is 20 msec for the experiment of *a* and *b*; 40 sec for that of records 1–6.

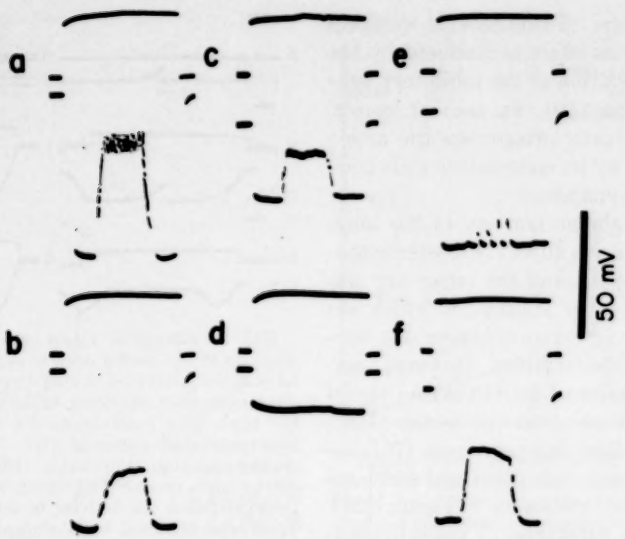


FIG. 21. The effects of GABA (10^{-7} w/v) on the p.s.p.'s of a lobster muscle fiber. The responses are shown during the hyperpolarization of the membrane by an applied current which was the same for all the records, as shown by the current trace. *a:* e.p.s.p.'s at 25/sec; *b,* i.p.s.p.'s at 100/sec; *c, d,* about 4 and 15 sec respectively after applying GABA; *e, f,* about 1 min after washing out the GABA. The stimulation frequency for the excitatory axon was decreased to 10/sec. The smaller hyperpolarizations produced by the current in *c* and *d* denote the lowered membrane resistance of the muscle fiber. The effect of the GABA was greater in the later recording (*d*). (From 50).

trophysiological phenomena of invertebrate and vertebrate excitable systems has been illustrated in a number of examples. Pharmacologically, however, many invertebrate synapses appear to differ fundamentally from those of vertebrates. For example, the electrophysiological properties of the squid giant axon synapse (9–11, 52) and of the neuromuscular junctions of the grasshopper, *Romalea microptera* (15, 16) are identical with those of other invertebrate and vertebrate synapses (40, 46). Pharmacologically, however, they do not appear to resemble other varieties (9, 65) in either vertebrates (45) or invertebrates (89).

Action of drugs on some crustacean synapses. A possible clue to this difficulty is offered by recent studies of the actions of amino acid drugs on crustacean synapses (7, 49, 50, 60). In the most extensive study, that on lobster neuromuscular synapses (50) excitatory and inhibitory synaptic activity, membrane potentials and membrane conductance were examined simultaneously with intracellular recordings. GABA and other substances, which in the cat cortex block depolarizing axodendritic synapses, in the lobster muscle fibers activate the inhibitory (Figure 21). The resting potential is little affected, as may be expected from the known electrophysiology of crustacean synapses (25). The intense activation of inhibitory synapses is evidenced, however, by a marked decrease in membrane resistance (Figure 22) and time constant. These effects diminish and shorten the excitatory p.s.p.'s and thereby prevent or hinder their summation (Figure 23). The excitatory action of these depolarizations upon the gradedly responsive muscle fibers is thereby diminished or abolished. These effects of the drugs are reversible (Figures 21, 22).

Picrotoxin, which antagonizes the action of GABA in the crayfish stretch receptors (22) and blocks inhibition in crayfish muscles (82), also antagonizes the actions of

GABA in lobster neuromuscular synapses (Figure 24). This effect is produced by the selective inactivation of the inhibitory synaptic membrane (50). In the cat cortex, however, picrotoxin antagonizes the action of GABA (76) by its competitive activation of excitatory synapses.

Neither strychnine nor any of the long-chain ω-amino acids affect the lobster neuromuscular synapses, and the latter are also unaffected by other substances which act powerfully on vertebrate synapses (*e.g.* acetylcholine, d-tubocurarine). However, carnitine, (the betaine of β-OH GABA) one of the compounds which in cat cortex blocks selectively the inhibitory synapses (76), depolarizes lobster muscle fibers and decreases the membrane resistance (Figure 25). Therefore, this substance, or some byproduct, activates the excitatory neuromuscular synapses of the lobster.

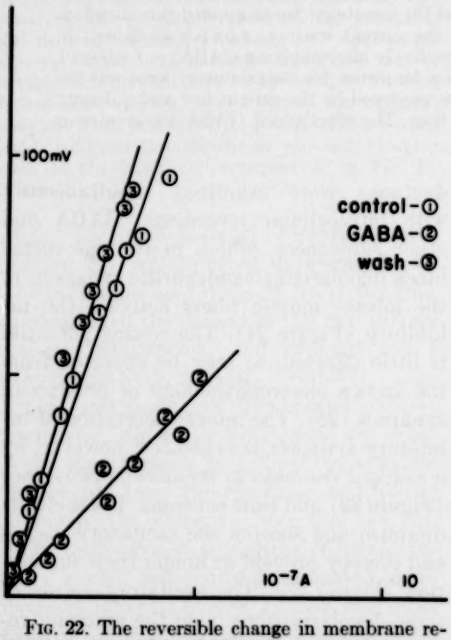


FIG. 22. The reversible change in membrane resistance produced by GABA. Same lobster muscle fibers as in Figure 20. Decreased resistance (higher conductance) is denoted by the lower slope of the line fitted to the experimental data. In this and subsequent graphs the ordinate represents the membrane voltage (in mv) produced by a hyperpolarizing pulse as given on the abscissa in 10^{-7} A units. (From 50).

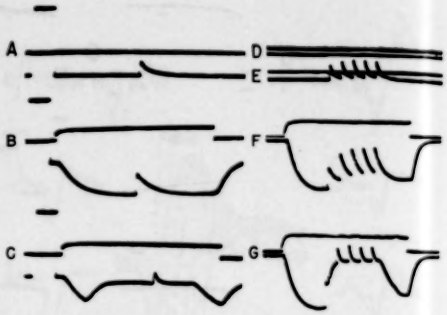


FIG. 23. Effects of i.p.s.p. on e.p.s.p. A single stimulus to the exciter axon evoked a large e.p.s.p. (*A*). When produced during hyperpolarization of the muscle fiber, the decay of the e.p.s.p. had about the same time constant as did the onset of the hyperpolarizing potential (*B*). Although at the resting potential stimulation (100/sec) of the inhibitor axon produced no i.p.s.p.'s (*D*), during hyperpolarization the activity of the inhibitory synapses was disclosed by a clamping action which drove the membrane potential almost back to the resting level (*C*, *G*). The e.p.s.p. evoked during this inhibitory activity was not only smaller, but also briefer (*C*). When a train of e.p.s.p.'s was produced during the i.p.s.p. the summation that was prominent on stimulating the exciter axon at 10/sec (*E*, *F*) was eliminated (*G*). The first e.p.s.p. of the train, produced at the onset of the i.p.s.p., was not affected. The amplitudes of the shortened e.p.s.p.'s were about the same size as in the unpolarized muscle fiber (*E*), but much smaller than in the hyperpolarized (*F*). Fluctuations in the size of the individual e.p.s.p.'s (*G*), that were more marked in other records, were probably due to different phase relations of the individual excitatory and inhibitory p.s.p.'s. The 50 mv calibrating square pulses represent 100 msec for *A–C* and 200 msec in *D–G*. (From 50).

Relation between crustacean and cat synapses. Thus, a number of substances which are known to act in the cat cortex in relatively specific ways (76) also act specifically in neuromuscular synapses of the lobster (50), but the actions are doubly inverted (Table 5). This finding suggests that the membranes of the respective synapses have some relations in chemical structure which in certain aspects must be closer than are the relations between axodendritic and axosomatic synapses in the cat. In other respects, however, the two latter synaptic va-

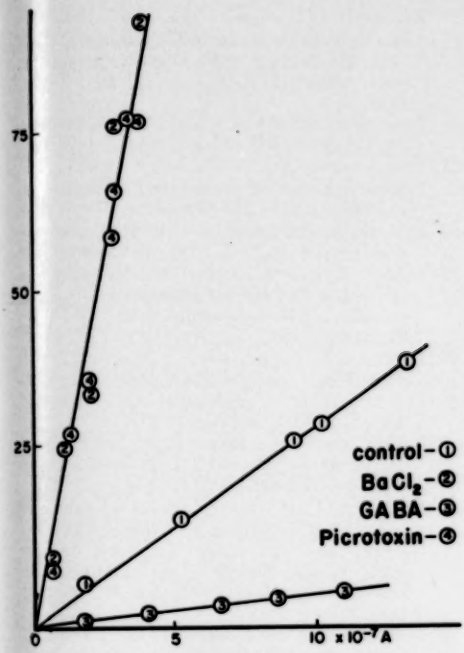


FIG. 24. Interaction of GABA and picrotoxin. GABA was applied in this experiment after the membrane resistance had been increased about 8-fold by substituting Ba^{++} for half the Na^{+} in the bathing solution. GABA decreased the membrane resistance about 50-fold. Picrotoxin reversed the action of GABA. (From 50).

rieties are more nearly alike, since they both differ from the lobster neuromuscular synapses in their common sensitivity to acetylcholine, d-tubocurarine and strychnine.

Data of this type therefore offer promise of disclosing various systematic classifying relationships from which it might eventually be possible to deduce the chemical natures of the structures of synaptic membranes. Further relations, with some evolutionary implications are also indicated by these findings (45). The arthropods are believed to have arisen from polyphyletic stems (87). Thus, the different pharmacological sensitivities of lobster, grasshopper, and squid synapses may indicate that pharmacologically divergent strains of membranes are involved in evolutionary development.

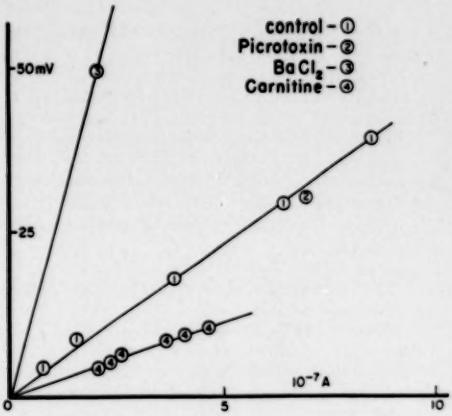


FIG. 25. Effect of carnitine on membrane resistance. The initial membrane resistance was not affected by strong picrotoxin (10^{-3} w/v), and the drug did not prevent increase of the membrane resistance by substituting Ba^{++} for half the Na^{+} of the bathing fluid. The decreased membrane resistance caused by carnitine was accompanied by depolarization of the fiber and contraction of the muscle. (From 50).

TABLE 5

Doubly Inverted Pharmacological Relations of Lobster Neuromuscular Synapses and of Cat Azodendritic Cortical Synapses, With Respect to Activator and Inactivator Drugs (After Ref. 50)

Animal	Drug Type	Synapse Type	
		Excitatory	Inhibitory
Lobster	Activator	Carnitine	GABA
	Inactivator	?	Picrotoxin
Cat	Activator	Picrotoxin	?
	Inactivator	GABA	Carnitine

REFERENCES

1. ALTAMIRANO, M., COATES, C. W. AND GRUNDFEST, H. Mechanisms of direct and neural excitability in electroplaques of electric eel. J. Gen. Physiol., **38**: 319–360, 1955.
2. ALTAMIRANO, M., COATES, C. W., GRUNDFEST, H. AND NACHMANSOHN, D. Electric activity in electric tissue. III. Modification of electrical activity of acetylcholine and related compounds. Biochim. et biophys. acta, **16**: 449–463, 1955.
3. ALTAMIRANO, M. AND GRUNDFEST, H. Three excitable systems of the synaptic unit in the innervated electroplaque preparation. Tr. Am. Neurol. A., **79**: 79, 1954.
4. AXELSSON, J. AND THESLEFF, S. A study on

supersensitivity in denervated mammalian skeletal muscle. J. Physiol., **144:** 31P, 1958.

5. Bennett, M. V. L. and Grundfest, H. Electrophysiology of electric organ in *Gymnotus carapo*. J. Gen. Physiol., **42:** 1067–1104, 1959.
6. Bennett, M. V. L., Grundfest, H. and Keynes, R. D. The discharge mechanisms of the electric cat-fish. J. Physiol., **143:** 52–53P, 1958.
7. Boistel, J. and Fatt, P. Membrane permeability change during inhibitory transmitter action in crustacean muscle. J. Physiol., **144:** 176–191, 1958.
8. Brock, L. G., Coombs, J. S. and Eccles, J. C. The recordings of potentials from motoneurones with an intracellular electrode. J. Physiol., **117:** 431–460, 1952.
9. Bryant, S. H. Transmission in squid giant synapses. The importance of oxygen supply and the effect of drugs. J. Gen. Physiol., **41:** 473–484, 1958.
10. Bryant, S. H. The function of proximal synapses of the squid stellate ganglion. J. Gen. Physiol., **42:** 609–616, 1959.
11. Bullock, T. H. and Hagiwara, S. Intracellular recording from the giant synapse of the squid. J. Gen. Physiol., **40:** 565–578, 1957.
12. Cajal, S. Ramón y. *Neuron Theory or Reticular Theory?* Consejo Superior de Investigaciones Cientificas Instituto "Ramón y Cajal," Madrid, 1954.
13. Castillo, J. del and Katz, B. Biophysical aspects of neuromuscular transmission. Progr. Biophys., **6:** 121–170, 1956.
14. Castillo, J. del and Katz, B. Modifications de la membrane produites par des influx nerveux dans la region du pace-maker du coeur. In *Microphysiologie Comparee des Elements Excitables*. Collog. Int. C.N.R.S. No. 67, Paris, 1957.
15. Cerf, J., Grundfest, H., Hoyle, G. and McCann, F. Neuromuscular transmission in the grasshopper *Romalea microptera*. Biol. Bull., **113:** 338, 1957.
16. Cerf, J., Grundfest, H., Hoyle, G. and McCann, F. The mechanism of dual responsiveness in muscle fibers of the grasshopper, *Romalea microptera*, J. Gen. Physiol. In press.
17. Drill, V. A. ed. *Pharmacology in Medicine*. McGraw Hill, New York, 1954.
18. Eccles, J. C. *The Physiology of Nerve Cells*. The Johns Hopkins Press, Baltimore, 1957.
19. Eccles, J. C., Fatt, P. and Koketsu, K. Cholinergic and inhibitory synapses in a pathway from motor-axon collaterals to motoneurones. J. Physiol., **126:** 524–562, 1954.
20. Eccles, J. C. and O'Connor, W. J. Responses which nerve impulses evoke in mammalian striated muscle. J. Physiol., **97:** 44–102, 1939.
21. Eccles, R. M. Intracellular potentials recorded from a mammalian sympathetic ganglion. J. Physiol., **130:** 572–584, 1956.
22. Elliott, K. A. C. and Florey, E. Factor I—inhibitory factor from brain. J. Neurochem., **1:** 181–192, 1956.
23. Eyzaguirre, C. and Kuffler, S. W. Processes of excitation in the dendrites and in the soma of single isolated nerve cells of the lobster and crayfish. J. Gen. Physiol., **39:** 87–119, 1955.
24. Fatt, P. Biophysics of junctional transmission. Physiol. Rev., **34:** 674–710, 1954.
25. Fatt, P. and Katz, B. The effect of inhibitory nerve impulses on a crustacean muscle fiber. J. Physiol., **121:** 374–489, 1953.
26. Fessard, A. and Matthews, B. H. C. Unitary synaptic potentials. J. Physiol., **95:** P9, 1939.
27. Florey, E. and McLennan, H. The effects of factor I and of gamma aminobutyric acid on smooth muscle preparations. J. Physiol., **145:** 66–76, 1959.
28. Fulton, J. F., ed. *Textbook of Physiology*. 17th ed. Oxford Univ. Press, London 1955.
29. Fuortes, M. G. F. Discussion. Am. J. Ophth., **46:** 13–16, 1958.
30. Gaffey, C. T. and Mullins, L. J. Ion fluxes during the action potential in *Chara*. J. Physiol., **144:** 505–524, 1958.
31. Gaskell, W. H. On the action of muscarin upon the heart and on the electrical changes in the non-beating cardiac muscle brought about by stimulation of the inhibitory and augmentor nerves. J. Physiol., **8:** 404–414, 1887.
32. Goodman, L. S. and Gilman, A. *The Pharmacological Basis of Therapeutics*. 2nd ed. Macmillan, New York, 1955.
33. Granit, R. *Receptors and Sensory Perception*. Yale Univ. Press, New Haven, 1955.
34. Granit, R. Introductory remarks. In *Electrophysiology of Vision*, pp. 505–506. National Physical Lab. London, 1958.
35. Grundfest, H. Some properties of excitable tissue. In *Fifth Conference on the Nerve Impulse*. Josiah Macy, Jr. Found., New York, 1956.
36. Grundfest, H. Excitation at synapses. J. Neurophysiol., **20:** 316–324, 1957.
37. Grundfest, H. Excitation triggers in post-junctional cells. In *Physiological Triggers*. American Physiological Society, Washington, D.C., 1957.
38. Grundfest, H. General Problems of drug action on bioelectric phenomena. Ann. New York Acad. Sci., **66:** 537–591, 1957.
39. Grundfest, H. The mechanisms of discharge of the electric organ in relation to general and comparative electrophysiology. Progr. Biophys., **7:** 1–85, 1957.
40. Grundfest, H. Electrical inexcitability of synapses and some of its consequences in the central nervous system. Physiol. Rev., **37:** 337–361, 1957.
41. Grundfest, H. An electrophysiological basis for cone vision in fish. Arch. ital. biol., **96:** 135–144, 1958.
42. Grundfest, H. Designated discussion. In *Reticular Formation of the Brain*, pp. 473–487. Little, Brown & Co., Boston, 1958.

43. Grundfest, H. Discussion in: *Electrophysiology of the Visual System*. Am. J. Ophth., **4**: (3) Sept., 1958.
44. Grundfest, H. Electrophysiology and pharmacology of dendrites. Electroencephalog. & Clin. Neurophysiol., Suppl. **10**: 22–41, 1958.
45. Grundfest, H. An electrophysiological basis for neuropharmacology. Fed. Proc., **17**: 1006–1018, 1958.
46. Grundfest, H. Synaptic and ephaptic transmission. In Handbook of Physiology. Neurophysiology I. American Physiological Society, Washington, D. C., 1959.
47. Grundfest, H. Evolution of conduction in the nervous system. In *Evolution of Nervous Control from Primitive Organisms to Man*. Amer. Assoc. for the Advancement of Science, Washington, D. C., 1959.
48. Grundfest, H. and Purpura, D. P. Modes of action of curare and other synapse inactivators in the central nervous system. In *Proc. Symp. on Curare and Curarizing Substances*. Elseviers, Amsterdam, 1959.
49. Grundfest, H., Reuben, J. P. and Rickles, W. H., Jr. Electrophysiology and pharmacology of lobster muscle fibers. Biol. Bull., **115**: 332, 1958.
50. Grundfest, H., Reuben, J. P. and Rickles, W. H., Jr. The electrophysiology and pharmacology of lobster neuromuscular synapses. J. Gen. Physiol. In press.
51. Grusser, O. J. Rezeptorpotentiale einzelner retinaler Zapfen der Katze. Naturwiss., **19**: 44, 1957.
52. Hagiwara, S. and Tasaki, I. A study of the mechanism of impulse transmission across the giant synapse of the squid. J. Physiol., **143**: 114–137, 1958.
53. Hobbiger, F. Effects of γ-aminobutyric acid on the isolated mammalian ileum. J. Physiol., **142**: 147–164, 1958.
54. Hodgkin, A. L. The Croonian Lecture. Ionic movements and electrical activity in giant nerve fibres. Proc. Roy. Soc. London Ser. B, **148**: 1–37, 1958.
55. Hodgkin, A. L. and Huxley, A. F. A quantitative description of membrane current and its applications to conduction and excitation in nerve. J. Physiol., **117**: 500–544, 1952.
56. Huxley, A. F. Muscle structure and theories of contraction. Progr. Biophys., **7**: 255–318, 1957.
57. Jansen, J., Jr. Afferent impulses to the cerebellar hemispheres from the cerebral cortex and certain subcortical nuclei. Acta physiol. scandinav., **41**: Suppl. 143, 1–99, 1957.
58. Katz, B. The properties of the nerve membrane and its relation to the conduction of impulses. Symposia Soc. Exper. Biol., **6**: 16–38, 1952.
59. Katz, B. and Thesleff, S. The interaction between edrophonium (tensilon) and acetylcholine at the motor end-plate. Brit. J. Pharmacol., **12**: 260–264, 1957.
60. Kuffler, S. W. and Edwards, C. Mechanism of gamma aminobutyric acid (GABA) action and its relation to synaptic inhibition. J. Neurophysiol., **21**: 588–610, 1958.
61. Liley, A. W. The effects of presynaptic polarization on the spontaneous activity at the mammalian neuromuscular junction. J. Physiol., **134**: 427–443, 1956.
62. Loewi, O. Ueber humorale Uebertragbarkeit der Herznervenwirkung. Arch. ges. Physiol., **189**: 239–242, 1921.
63. Lundberg, A. The electrophysiology of the submaxillary gland of the cat. Acta physiol. scandinav., **35**: 1–25, 1955.
64. MacNichol, E. J., Jr. and Svaetichin, G. Electric responses from the isolated retinas of fishes. Am. J. Ophth., **46**: 26–46, 1958.
65. McCann, F. V., Werman, R. and Grundfest, H. Graded and all-or-none electrical activity in insect muscle fibers. Biol. Bull., **115**: 356, 1958.
66. Monnier, A. M. Physical and chemical aspects of neuromuscular transmission. Cold Spring Harb. Symp. Quant. Biol., **4**: 111–131, 1936.
67. Oikawa, T., Ogawa, T. and Motokawa, K. Origin of so-called cone action potentials. J. Neurophysiol., **22**: 102–111, 1959.
68. Parker, G. H.: *The Elementary Nervous System*. Lippincott, Philadelphia, 1919.
69. Purpura, D. P. Organization of excitatory and inhibitory synaptic electrogenesis in the cerebral cortex. In *Reticular Formation of the Brain*, pp. 435–457. Little, Brown & Co., Boston, 1958.
70. Purpura, D. P. Nature of electrocortical potentials and synaptic organizations in cerebral and cerebellar cortex. Internat. Rev. Neurobiol., **1**: 1959. In press.
71. Purpura, D. P., Girado, M. and Grundfest, H. Selective blockade of excitatory synapses in the cat brain by γ-aminobutyric acid (GABA). Science, **125**: 1200–1202, 1957.
72. Purpura, D. P., Girado, M. and Grundfest, H. Mode of action of aliphatic amino acids on cortical synaptic activity. Proc. Soc. Exper. Biol. & Med., **95**: 791–796, 1957.
73. Purpura, D. P., Girado, M. and Grundfest, H. Central synaptic effects of ω-guanidino acids and amino acid derivatives. Science, **127**: 1179–1180, 1958.
74. Purpura, D. P., Girado, M. and Grundfest, H. Synaptic components of cerebellar electrocortical activity evoked by various afferent pathways. J. Gen. Physiol., **42**: 1037–1066, 1959.
75. Purpura, D. P., Girado, M. and Grundfest, H. Components of evoked potentials in cerebral cortex. Electroencephalog. & Clin. Neurophysiol. In press.
76. Purpura, D. P., Girado, M., Smith, T. G., Callan, D. A. and Grundfest, H. Structure-activity relations of amino acids and derivatives on central synapses. J. Neurochem., **3**: 238–268, 1959.

77. Purpura, D. P., Girado, M., Smith, T. G. and Gomez, J. A. Synaptic effects of systemic γ-aminobutyric acid in cortical regions of increased vascular permeability. Proc. Soc. Exper. Biol. & Med., **97**: 348–353, 1958.

78. Purpura, D. P., Girado, M., Smith, T. G. and Gomez, J. A. Effects of systemically administered ω-amino acid and guanidino acids on spontaneous and evoked cortical activity in regions of blood-brain barrier destruction. Electroencephalog. & Clin. Neurophysiol., **10**: 677–685, 1958.

79. Purpura, D. P. and Grundfest, H. Nature of dendritic potentials and synaptic mechanisms in cerebral cortex of cat. J. Neurophysiol., **19**: 573–595, 1956.

80. Purpura, D. P. and Grundfest, H. Physiological and pharmacological consequences of different synaptic organizations in cerebral and cerebellar cortex. J. Neurophysiol., **20**: 494–522, 1957.

81. Purpura, D. P. and Grundfest, H. Comparative pharmacological analysis of different hippocampal synaptic organizations (cat). Fed. Proc., **18**: 123, 1959.

82. Robbins, J. and Van der Kloot, W. G. The effect of picrotoxin on peripheral inhibition in crayfish. J. Physiol., **143**: 541–552, 1958.

83. Schaeffer, H. and Haas, P. Uber einen lokalen Erregungstrom aus der motorischen Endplatte. Arch. ges. Physiol., **242**: 364–381, 1959.

84. Shanes, A. M. Electrochemical aspects of physiological and pharmacological actions in excitable cells. Pharmacol. Rev., **10**: 59–273, 1958.

85. Sigg, E. and Grundfest, H. Pharmacological differences of similarly electrogenic neuraxial sites of bullfrog. Amer. J. Physiol. In press.

86. Takahashi, H., Tiba, M., Yamazaki, T. and Noguchi, F. On the site of action of γ-aminobutyric acid on blood pressure. Jap. J. Physiol., **8**: 378–390, 1958.

87. Tiegs, O. W. and Manton, S. M. The evolution of the arthropoda. Biol. Rev., **33**: 255–337, 1958.

88. Tomita, T. A study on the origin of intraretinal action potential of the cyprinid fish by means of pencil-type microelectrodes. Jap. J. Physiol., **7**: 80–85, 1957.

89. Welsh, J. H. Serotonin as a possible neurohumoral agent: Evidence obtained in lower animals. Ann. New York Acad. Sci., **66**: 618–630, 1957.

90. Wiesel, T. N. Recording inhibition and excitation in the cat's retinal ganglion cells with intracellular electrodes. Nature, London, **183**: 264–265, 1959.

NEUROMYOSITIS

KEVIN D. BARRON, M.D.[1] AND DAVID I. M. FINE, M.D.[2]

Senator (16, 17) and Gowers (6) introduced the concept that peripheral neuritis may occur in dermatomyositis and the related entity of polymyositis. They considered the nerve lesions to be part of the same disease process which affects skin and muscle. The terms neuromyositis and dermatoneuromyositis derive from their reports. In point of fact, the modern reader of Senator's case histories cannot arrive at definitive diagnoses from the clinical and anatomical information presented. Further, Senator did not describe inflammation of nerves, where these were available for histological examination. Gowers provided no satisfactory evidence for his assumption that polyneuritis was a frequent accompaniment of polymyositis. Nevertheless, the terms neuromyositis and dermatoneuromyositis have persisted, despite the fact that later investigators failed to provide an anatomical basis for the clinical entity. In recent years, the meaning and validity of these syndromes has been a subject of considerable debate (1, 5, 15, 18).

This paper will report two cases of dermatomyositis in which signs and symptoms of symmetric polyneuropathy developed in the course of the disease. In one, anatomical evidence of a true polyneuritis was obtained at autopsy.

CASE REPORTS

CASE 1.

The patient was a 56 year old white spinster. Apart from recurrent episodes of right upper quadrant discomfort and mild fatty food intolerance, she was well until April of 1955. In that month she developed severe pains in the muscles of the back and extremities and rapidly progressive muscular weakness and stiffness. The motor difficulty was most severe in the shoulder and hip girdle musculature. Concomitantly, a diffuse, erythematous, facial rash and swelling of the eyelids occurred.

For these complaints the patient was admitted to another hospital in May, 1955. There, a clinical diagnosis of dermatomyositis was supported by a skin and muscle biopsy. In spite of meticorten therapy, her condition gradually worsened. She developed a generalized erythematous rash which lasted two to three weeks and recurred several times. The facial rash was persistent.

Following discharge from the hospital in August, 1955, the patient noted occasional dysphagia, especially for solid foods, and a twenty pound weight loss. However, she did not experience fever or joint pain. By December, 1955, her weakness had progressed so that only occasionally was she able to walk with support. She became bed-confined and was admitted to Montefiore Hospital in February, 1956.

Pertinent physical findings included normal temperature, pulse and respirations. She was normotensive and remained so. There was diffuse facial erythema and edema of the eyelids. The joints were normal. Neurological examination revealed active and equal tendon and superficial abdominal reflexes. There were no abnormal reflexes. There was generalized weakness of all muscle groups of the limbs, trunk and neck, most striking in the proximal muscles of the upper limbs. All affected muscles were painful to pressure and manipulation. Atrophy of the shoulder musculature was found. Sensation was intact.

Laboratory tests including urinalysis,

[1] The Henry and Lucy Moses Research Laboratories of the Laboratory Division, Montefiore Hospital, New York, N. Y. The support and assistance of Dr. Harry M. Zimmerman in this investigation are gratefully acknowledged.

[2] Trainee of The National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service.

complete blood count, and repeated lupus preparations were normal. Roentgenograms of the chest and the electrocardiogram were unremarkable. An esophagram was reported as showing an "abnormal swallowing mechanism, which can be considered compatible with the diagnosis of dermatomyositis." An electromyogram showed an occasional complex voluntary potential during minimal contraction and a partial interference pattern during maximal activity. Twenty-four hour urinary creatine excretion was 837 mg. and urinary creatinine over the same period was 876 mg.

The patient remained in Montefiore Hospital until her death one year later. In March, 1956, she underwent an uneventful cholecystectomy for acute cholecystitis. In October, 1956, she had an episode of right-sided obstructive uropathy associated with chills, fever and shock. She recovered following a right nephrolithotomy. Thereafter, she was maintained on furadantin 400 mg. daily until January, 1957, when the dose was reduced to 100–200 mg. daily.

During the first two months of hospitalization the patient received meticorten in doses varying from 5 to 20 mg. per day. No improvement occurred and on April 27, 1956, dosage was increased to 50 mg. per day. The patient then showed a generalized increase in muscle power and, on occasion, was able to stand in a walker. This improvement was only temporary, however, and a steady, slow deterioration ensued. Muscular pains were a continuing prominent complaint. Dysphagia was only occasionally noted and her nourishment was adequate. She received supplementary oral and paren-

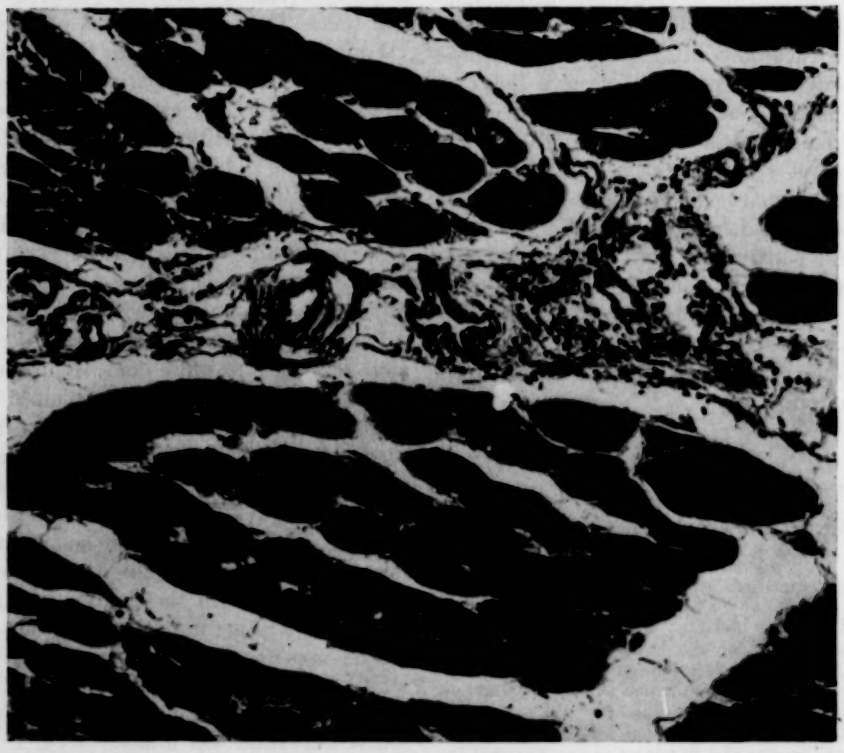


FIG. 1. Case 1. Section of thigh muscle. The sarcoplasm of some fibers is homogeneous. There is a collection of lymphocytes in the perimysium. Hematoxylin-eosin, × 150.

teral vitamins. Neither contractures nor decubiti developed.

On January 11, 1957, a bullous eruption appeared on the limbs and trunk, and an increase of muscular pain and weakness was noted. Meticorten was increased to 100 mg. daily and hydrocortisone was administered intravenously. On January 30, 1957, the patient first complained of "numbness and coldness" throughout the extremities. There was pain in the lower limbs radiating in a sciatic distribution. Examination on January 31 disclosed areflexia; loss or impairment of all sensory modalities in both lower limbs to mid-thigh; hypalgesia and hypesthesia in the upper limbs to the elbows. Subsequent neurologic evaluation was not recorded. On February 4, overflow urinary incontinence was observed and catheterization yielded "more than 500 cc." of urine.

Episodes of shock, dyspnea and tachycardia ensued and death occurred on February 12, 1957.

Autopsy findings included left renal lithiasis and the scar of a right nephrolithotomy; bilateral adrenal cortical atrophy; generalized osteoporosis and bilateral, focal pneumonia. There was a cholecystectomy scar. Multiple sections of skin showed atrophy of the epidermis and focal, lymphocytic infiltrates in the dermis. There was some hyalinization of dermal connective tissue.

The striking neuropathologic findings were microscopic and limited to the muscles, peripheral nerves and spinal cord. The brain was normal.

Sections of muscle were obtained from all limbs. These showed focal atrophy of fibers, accompanied by proliferation of sarcolemmal nuclei and loss of cross-striations. Monocytic infiltrates (Figures 1, 2) were particularly prominent in the psoas mus-

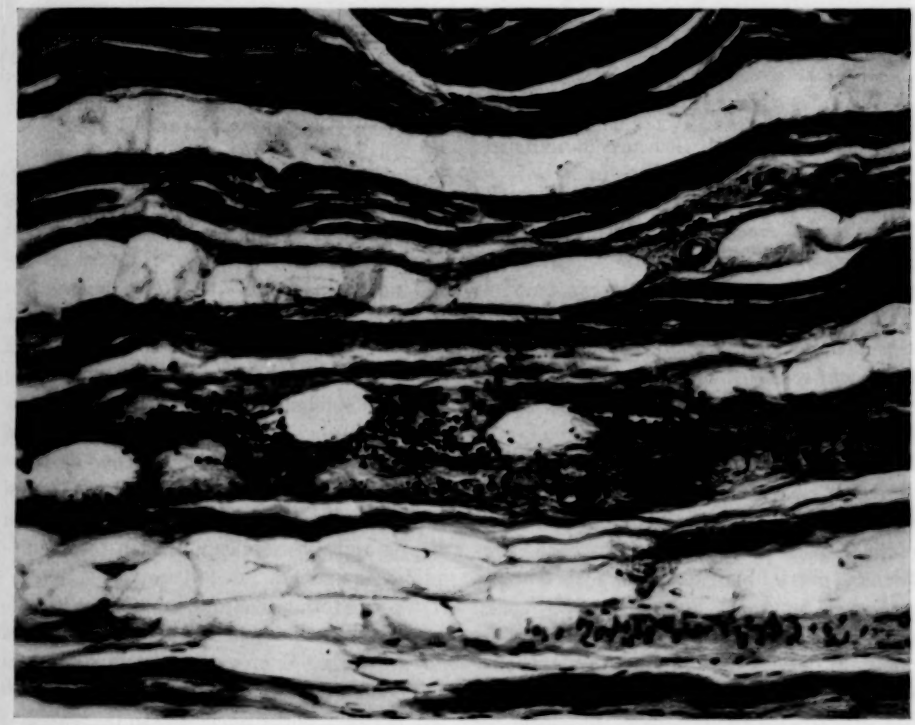


FIG. 2. Case 1. Psoas muscle. Note lymphocytic infiltration. Hematoxylin-eosin, × 120.

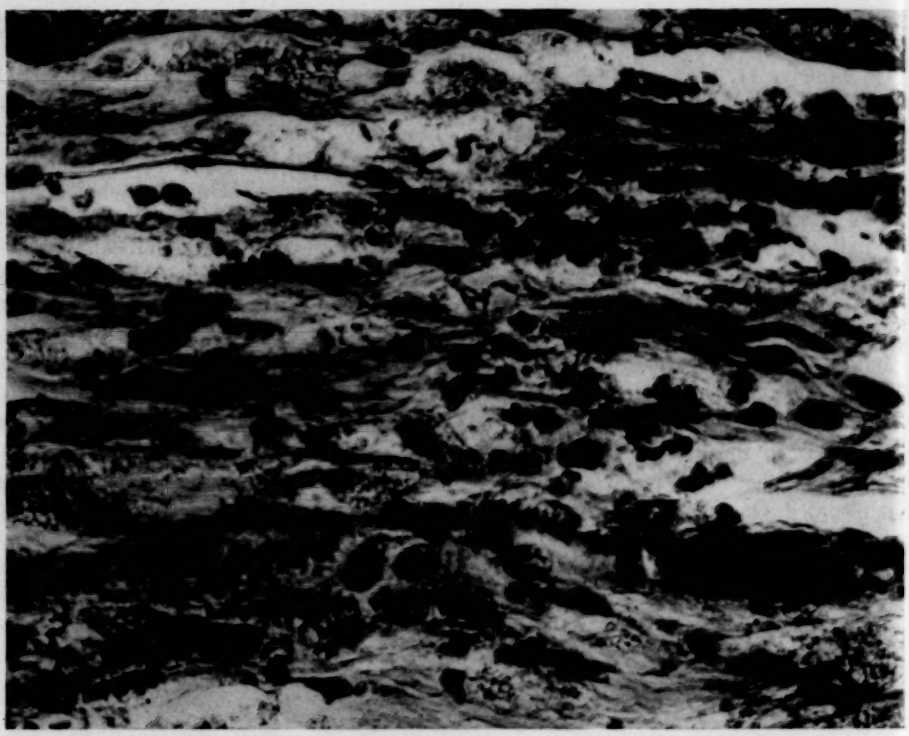


FIG. 3. Case 1. Right median nerve. Nerve fibers are infiltrated by polymorphonuclear leukocytes. Note also destruction of myelin sheaths and the presence of large nuclei with prominent nucleoli. Hematoxylin-eosin stain, × 440.

cles and consisted largely of lymphocytes. There were occasional histiocytes and plasma cells. Endomysial and perimysial connective tissue was increased in amount.

Both median and both popliteal nerves were removed and examined. In hematoxylin-eosin sections, the median nerves were heavily infiltrated by polymorphonuclear leukocytes (Figure 3). These appeared to lie within and between nerve fibers and were diffusely distributed throughout multiple sections. They were predominantly neutrophilic. Eosinophiles were very rare. Frequently, nerve fibers appeared pushed apart, and were separated by clear spaces which produced an edematous appearance. In the popliteal nerves, the inflammatory response was not nearly so conspicuous, and was limited to focal, lymphocytic, interfascicular infiltrates (Figure 4). There were many clusters of large, pale, round or oval nuclei in both the upper and lower extremity nerves (Figure 5). These nuclei frequently contained a prominent nucleolus and were thought to represent proliferating Schwann cells. The vasa nervorum were normal. Spielmeyer, Bielschowsky and Sudan IV preparations of both median and popliteal nerves disclosed extensive destruction of myelin sheaths (Figures 6, 7) and axis cylinders (Figure 8) associated with a heavy and diffuse accumulation of sudanophilic granules.

Cervical, thoracic and lumbosacral nerve roots were examined. They were infiltrated to a varying degree by lymphocytes and occasional plasma cells (Figure 9) which lay between nerve fibers and in perivascular

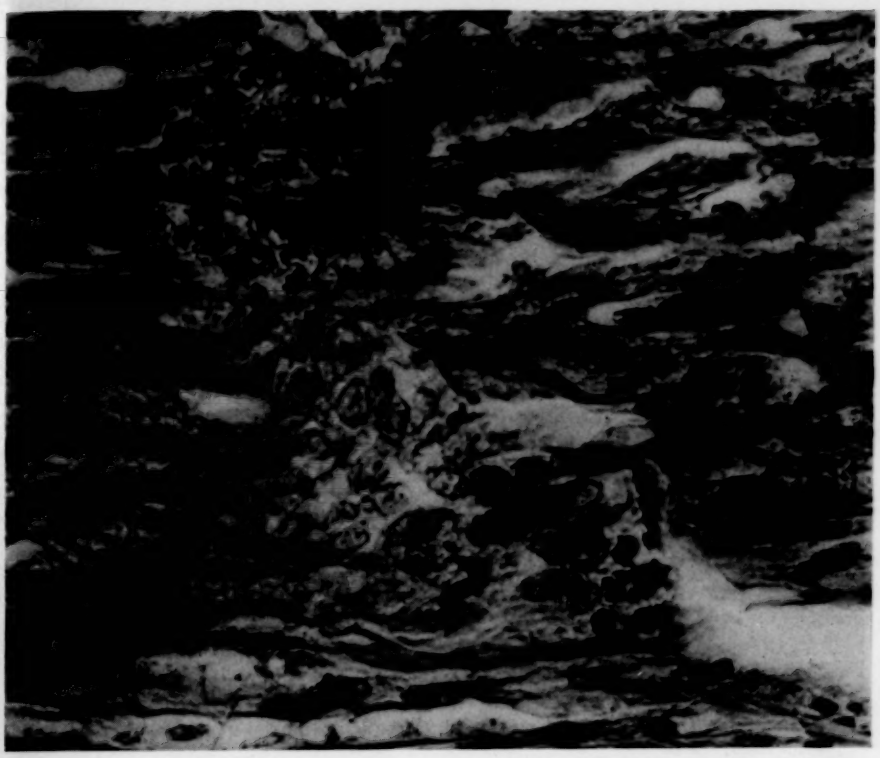


FIG. 4. Case 1. Left median nerve. Note the collection of pale nuclei and infiltration by polymorphonuclear leukocytes. Hematoxylin-eosin, × 440.

spaces. Lymphocytic infiltrates were most marked in lumbosacral posterior nerve roots where they were sometimes very dense. Of particular interest was the presence of an arteriolitis, which was limited to some of the posterior nerve roots (Figure 10). Occasional small arteries and arterioles showed fibrinoid degeneration of their walls or the medial coat appeared smudged and deeply eosinophilic. Such vessels were surrounded by lymphocytes or their walls were actually infiltrated by white blood cells. Spielmeyer and Bielschowsky stains of the nerve roots demonstrated a mild to moderate pathologic alteration of myelin and axons, but Sudan preparations were negative. Myelin and axis cylinder abnormalities were more advanced in the posterior lumbosacral roots. Only a single lumbar posterior root ganglion was available. It was histologically normal.

The spinal cord was examined at multiple levels by hematoxylin-eosin, Nissl, Spielmeyer and Sudan IV techniques. Although, as described, the posterior spinal nerve roots were abnormal, there was no ascending degeneration. Anterior horn cell neurones showed mild axonal change. At the lumbosacral level, there were a few, perivascular collections of lymphocytes in the leptomeninges and within the cord. The lumbar and thoracic posterior columns exhibited several, fresh, minute zones of malacia. These lesions contained sudanophilic substance, frequently located within macrophages. They were discontinuous and unassociated with astrocytic response, vascular alteration or inflammation. Their pathogenesis was not explained.

Case Comment. The patient developed a fulminant polyneuropathy during an ex-

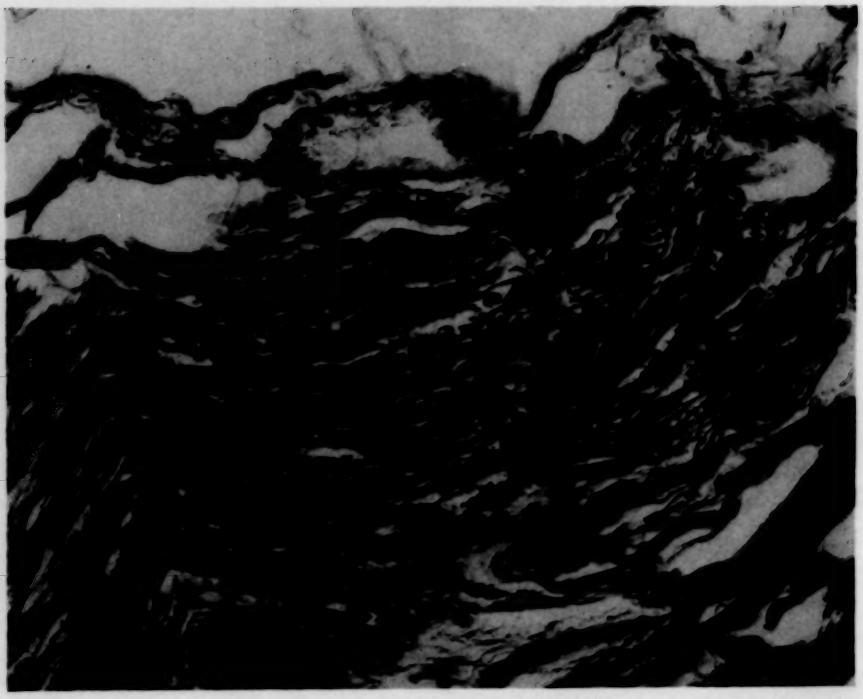


FIG. 5. Case 1. Right popliteal nerve. One of the loose, lymphocytic infiltrates. Hematoxylin-eosin, × 260.

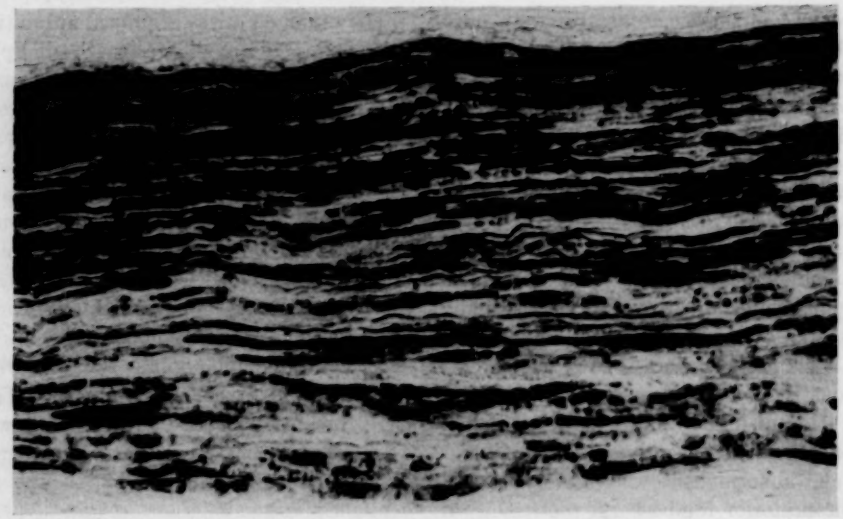


FIG. 6. Case 1. Right median nerve. Myelin sheaths are pale or shrunken and fragmented. There are scattered globules of degenerating myelin. Spielmeyer, × 150.

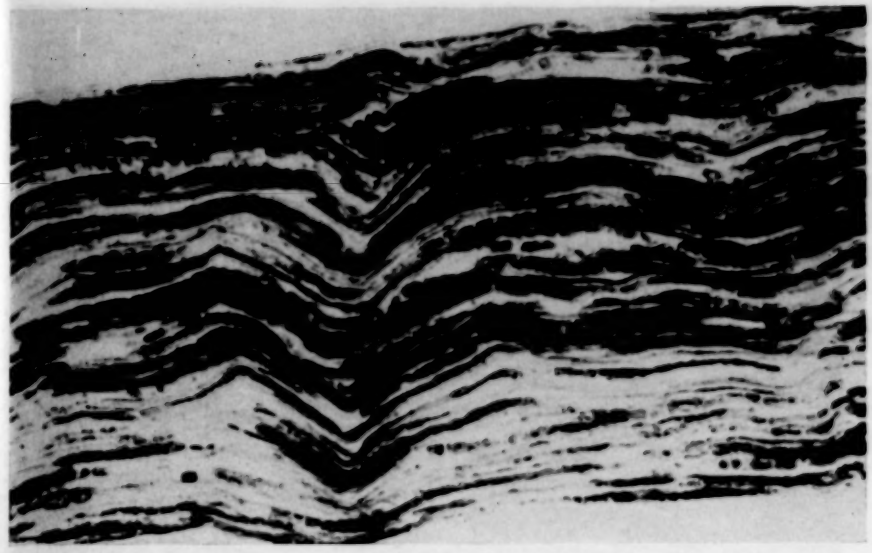


FIG. 7. Case 1. Left popliteal nerve. Myelin sheaths are diffusely abnormal. Spielmeyer, × 150.

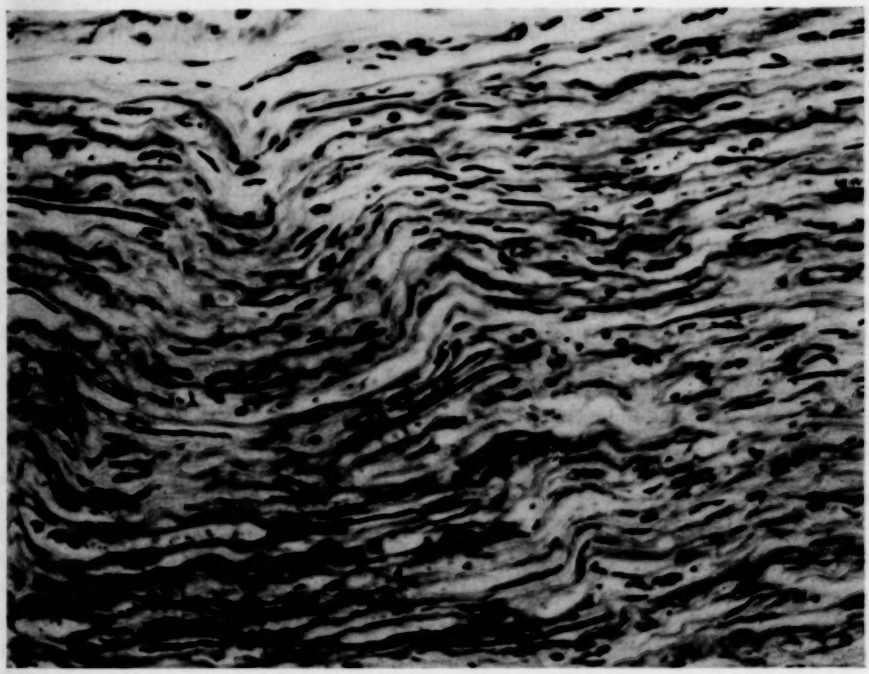


FIG. 8. Case 1. Right median nerve. Axons are irregularly thickened, fragmented and tortuous. Bielschowsky (paraffin-embedded), × 150.

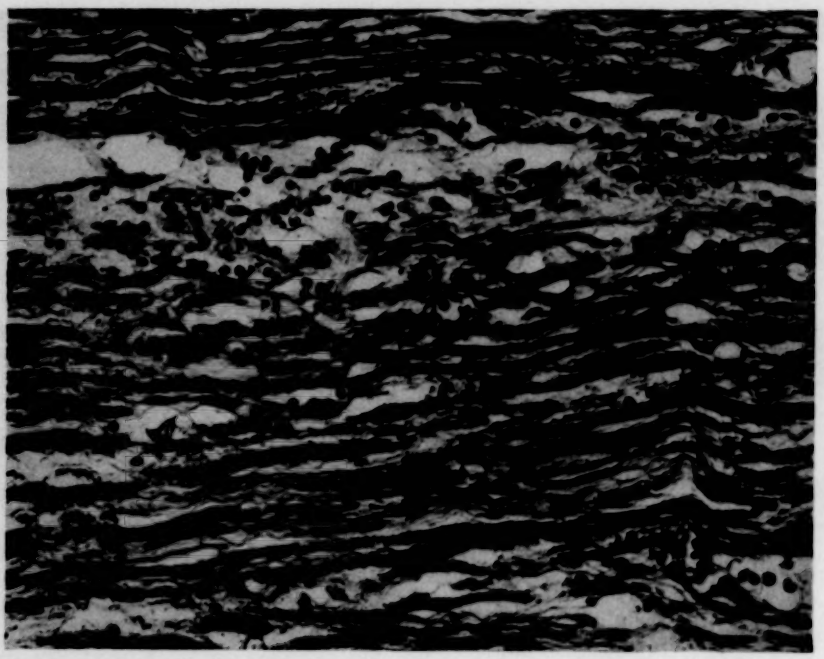


FIG. 9. Case 1. Posterior root of the Cauda Equina. Note lymphocytic infiltration. Hematoxylin-eosin, × 200.

acerbation of the cutaneous lesions. The fact that furadantin was administered over a prolonged period is recorded because neuropathy has developed during use of this drug (7, 11, 13) and the related compound, furacin (14, 19). In such instances, however, the neuropathy has invariably appeared within the first few weeks of treatment, and the dosage employed has been higher. Further, in the neuropathy accompanying furadantin treatment, the peripheral nerves do not show evidence of inflammation or angiitis (2, 8).

CASE 2.

This patient was a 14 year old white female who, in late November, 1955, developed generalized aching, weakness and stiffness of the limbs, "pins and needles" sensations in the feet, and a remittent temperature to 101° F. She was admitted to another hospital where laboratory studies including lumbar puncture and spinal fluid analysis, heterophile agglutinins, L.E. cell preparations, febrile agglutinins and blood cultures were entirely normal. Antibiotic therapy did not relieve symptoms. Because of rapidly progressive weakness of the limbs, a feature which quickly dominated the clinical picture, the patient was seen by a neurologist who advised and effected transfer to this institution on December 24th.

Physical examination showed normal vital signs, a palpable liver edge, mild axillary and cervical lymphadenopathy, and a grade II, untransmitted, apical, systolic murmur.

Neurologic examination showed absence of tendon reflexes, except for the ankle jerks which were present and equal. There was hypalgesia and hypesthesia over the fingers and toes. Position and vibratory sense were intact. There was moderate muscle tenderness throughout and striking proximal mus-

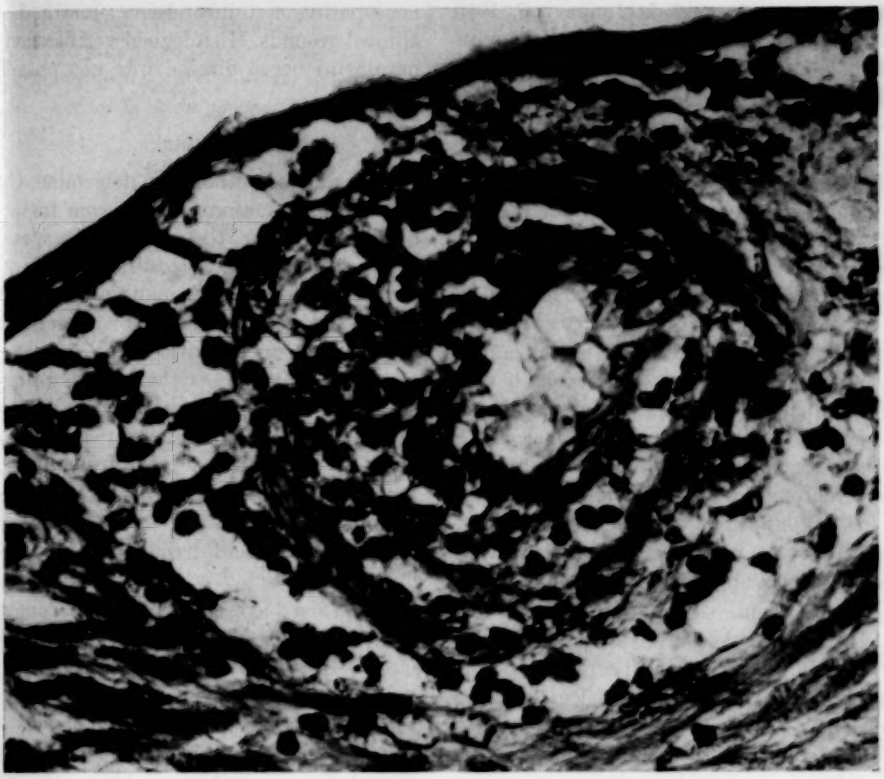


FIG. 10. Case 1. Posterior root of the Cauda Equina. Necrosis of the wall of a small artery and infiltration by leukocytes. Hematoxylin-eosin, × 540.

cle weakness, more marked in the pelvic girdle. The distal limb musculature was also paretic, particularly hand grip and the dorsiflexors of the wrists. She was able to sit up and to stand; but could walk only with aid, and then with a waddling gait.

Laboratory data, including urinalysis, complete blood counts, urinary porphyrins, trichinella complement fixation tests, and radioactive iodine uptake were normal. Urinary creatine excretion was 580 mg. per 24 hours, and creatinine excretion 469 mg. L.E. cell preparations were again negative.

On December 29th, a slightly raised, erythematous rash appeared on the right elbow. During the ensuing ten days, skin overlying the left elbow, both ankles and the anterior thighs became similarly involved. The eruption then became violaceous and slowly disappeared. As the rash subsided, edema of the face and conspicuous, diffuse swelling of the extremities, which pitted minimally, developed. The muscles became "doughy" in consistency. Tenderness and weakness progressed, and the patient was unable to sit or stand. Superficial sensation was now impaired to the elbows and mid-calves. Paresthesias of the limbs were a prominent complaint and dysesthesia was described on sensory testing over the finger tips. Dysuria and incontinence developed but proved temporary and were not investigated. There were remittent fever to 101–102° F. and persistent tachycardia at a rate of about 120.

Biopsy of skin and muscle from the right

thigh was performed on January 6, 1956. Microscopic examination of hematoxylin-eosin preparations disclosed infiltration of the superficial layers of the dermis by leukocytes. These were predominantly lymphocytes, but neutrophiles and a very occasional eosinophile could be discerned. The inflammatory cells were largely perivascular in distribution. The dermis was otherwise unremarkable, and the epidermis appeared normal. In the muscle sections isolated fibers showed deeply basophilic sarcoplasm and contained proliferating nuclei, among which mitotic figures were occasionally seen. These nuclei were sometimes oval, pale and large, and exhibited prominent nucleoli. On other occasions, they were elongated and hyperchromatic. The basophilic change was usually confined to short segments of individual fibers. Other changes included vacuolation of sarcoplasm, accumulation of histiocytes about sarcoplasmic debris and infiltration of the perimysium by lymphocytes. Biopsy of muscle from the left thigh on March 8, 1956, was histologically normal.

On January 9th, steroid therapy was begun. The patient received 30 mg. of meticorten daily for five weeks, and the dosage was then gradually reduced. There was pronounced reversal of the clinical course. After three days of treatment, fever and tachycardia subsided, and, after one week, muscle tenderness and swelling had largely disappeared. Improvement of muscle power followed, reflexes returned, and sensory alterations regressed. By April 2nd, muscle strength was normal. The patient was followed as an outpatient and meticorten was discontinued in September, 1956. She remained well but was lost to follow-up in a few months.

Case Comment. Severe paresthesias were an early and persistent complaint, and were accompanied by loss of sensation, areflexia and prominent distal weakness. In addition, there were classical signs of dermatomyositis. The diagnosis of a concomitant polyneuropathy certainly seems justified on clinical grounds. Histological verification of peripheral nerve disease was not possible, however.

DISCUSSION

As far as the authors can determine, Case 1 is the first anatomically proven instance of inflammation of the peripheral nerves accompanying dermatomyositis. In Case 2, a polyneuropathy, whose anatomical features could not be studied, was a presenting symptom in an otherwise typical example of dermatomyositis. Others have allowed that the peripheral nerves may be involved secondarily in dermatomyositis and polymyositis, as by trauma (1) from pressure in bedridden, cachectic patients, and by nutritional deficiency (9) accompanying the chronic course and frequently concurrent dysphagia. Obviously, the cases presented here did not have a traumatic neuropathy. Deficiency disease may be eliminated in Case 1 by the histologic characteristics of the lesions and by the fact that the patient was adequately nourished and received oral and parenteral multivitamin therapy. In Case 2, dietary intake was always adequate, the course to recovery was short, and dysphagia was never a symptom.

Clinical and anatomical evidence of polyneuritis is lacking in several, large, thoroughly studied series (3, 4, 12, 18) of dermatomyositis and polymyositis. The finding of "fibrillation potentials" during electromyographic examination, which is mentioned in several clinical series, cannot be interpreted as indicative of a neural lesion (10). In this institution, 17 instances of dermatomyositis have been observed in the past 15 years. Two of these are the basis of this report. The authors' experience is too small for statistical analysis, but the extensive series referred to above indicate that polyneuritis is rare in dermatomyositis.

If the term neuromyositis is used, it should be confined to patients in whom polyneuritis occurs in the course of poly-

myositis, and is accompanied by clinical signs of symmetric polyneuropathy. Where cutaneous lesions are evident, the designation *dermatoneuromyositis* may be preferred.

SUMMARY

Two cases of dermatomyositis accompanied by clinical signs of symmetric polyneuropathy are presented. One case was autopsied and a true polyneuritis found. The concept of neuromyositis is discussed. It is concluded that inflammation of peripheral nerves may occur in dermatomyositis. It would appear that the cutaneous, muscular and neural lesions are due to the same disease process.

REFERENCES

1. Adams, R. D., Denny-Brown, D. and Pearson, C. M. *Diseases of Muscle*, p. 312. P. B. Hoeber, Inc., New York, 1953.
2. Barron, K. D. Personal observations. 1958.
3. Christianson, H. B., Brunsting, L. A. and Perry, H. O. Dermatomyositis; unusual features, complications, and treatment. A. M. A. Arch. Dermat., **74:** 581–589, 1956.
4. Eaton, L. M. The perspective of neurology in regard to polymyositis. A study of 41 cases. Neurology, **4:** 245–263, 1954.
5. Garcin, R., Lapresle, R., Gruner, J. and Scherrer, J. Les polymyosites. Rev. neurol., **92:** 465–510, 1955.
6. Gowers, W. R. A lecture on polymyositis. Brit. M. J., **1:** 65, 1899.
7. Hasen, H. B. and Moore, T. D. Nitrofurantoin. J. A. M. A., **155:** 1470–1473, 1954.
8. Hyams, V. Personal communication. 1959.
9. Kinney, T. D. and Maher, M. M. Dermatomyositis. Am. J. Path., **16:** 561–594, 1940.
10. Lambert, E. H., Sayre, G. P. and Eaton, L. M. Electrical activity of muscle in polymyositis. Tr. Am. Neurol. A., **79:** 64–69, 1954.
11. Larsen, H. W. and Bertelsen, S. Neurologiske symptomer ved furadantinbehandling. Ugesk. laeger., **118:** 751–753, 1956.
12. O'Leary, P. A. and Waisman, M. Dermatomyositis; a study of 40 cases. Arch. Dermat. & Syph., **41:** 1001–1019, 1940.
13. Olivarius, B. de F. Polyneuropathi ved behandling med nitrofurantoin. Ugesk. laeger., **118:** 753–755, 1956.
14. Politano, V. A., Leadbetter, G. W. and Leadbetter, W. F. Use of furacin in treatment of testicular tumors; a case report. J. Urol., **79:** 771–774, 1958.
15. Rowland, L. P. Muscular dystrophies, polymyositis, and other myopathies. J. Chron. Dis., **8:** 510–535, 1958.
16. Senator, H. Ueber acute und subacute multiple neuritis und myositis. Ztschr. klin. Med., **15:** 61, 1889.
17. Senator, H. Ueber acute polymyositis und neuromyositis. Deutsche med. Wchnschr., **19:** 933, 1893.
18. Walton, J. N. and Adams, R. D. *Polymyositis*, p. 183. Williams & Wilkins Co., Baltimore, 1958.
19. Wildermuth, O. Testicular cancer: management of metastases with report of a new chemotherapeutic agent. Radiology, **65:** 599–602, 1955.

THE VALUE OF PHOTIC STIMULATION IN THE DIAGNOSIS OF EPILEPSY

S. MELSEN, M.D.[1]

Intermittent photic stimulation was introduced into electroencephalography in 1934 by Adrian and Matthews (1).

In 1946, Walter (13) demonstrated that photic stimulation may excite paroxysmal activity in epileptics.

The mechanism of action of photic stimulation has been the subject of much discussion. In a survey of this subject, Brazier (3) arrived at the result that, "the trigger mechanism may not lie on the specific visual pathway to the cortex but in that part of the system that leads through collaterals into the brain stem."

A large number of studies on the value of photic stimulation in the diagnosis of epilepsy have been published (4, 5, 6, 9, 10, 11, 15, 16, 17). The results of the various investigations are not directly comparable, partly because of differences in equipment and technique and partly because of heterogeneous clinical series.

Gastaut (6) found that paroxysmal abnormalities in the EEG can be provoked by photic stimulation in 10 to 20 per cent of all epileptics. Walter and Walter (15) observed abnormal response to photic stimulation in about 40 per cent of a series of epileptic patients. Buchthal and Lennox (4) reported that 15 per cent of epileptics and 1.4 per cent of normal individuals respond with paroxysmal abnormalities to photic stimulation.

It seems to be generally agreed that photic stimulation is most effective in cryptogenic (idiopathic) epilepsy and less so in the symptomatic variety. Hill (16) expressed the view that photic stimulation is of little aid in activation cortical epileptogenic foci; less than five per cent of patients with normal routine EEG yielded positive results. In most cases, the excited paroxysms were bilaterally synchronous, even when unilateral or focal cerebral abnormalities were suspected (6, 9).

In epileptic infants and children up to 15 years of age, Herrlin (9) found that the tendency to paroxysmal response to photic stimulation increased with the age. He also found that the occurrence of abnormal response was more frequent in girls than in boys, but the difference was not significant. Herrlin did not find that abnormal response to photic stimulation was more frequent in patients with abnormal than in those with normal routine EEG.

Gastaut (7) described a characteristic response which occurred particularly in combined provocation with photic stimuli and metrazol (photo-metrazol), but also in photic stimulation without administration of metrazol, *viz.* the so-called "recruiting response", which was accompanied by facial or generalized myoclonic jerks. Gastaut found a low myoclonic threshold in patients with idiopathic epilepsy, hysteria and schizophrenia. Bickford *et al.* (3) demonstrated that the size of the myoclonic response (measured as the average spike amplitude in m. orbicularis oculi) fell off in an exponential manner in relation to the distance of the light source. According to these authors, the photomyoclonic response is a normal reaction to photic stimulation when a high light intensity is used.

It is usually stated that stimulation with flicker frequencies of 12 to 20 per second is most effective. However, Laget and Humbert (10) found a correlation between the ages of the patients and the effective flicker frequency, low frequencies (3–8 f/s) being

[1] Departments of Neurology and Neurosurgery, Aarhus Municipal Hospital, University of Aarhus, Denmark.

more effective in children than higher ones (13–20 f/s). In photic activation first with increasing frequency (3–20 f/s) and then with decreasing frequency (20–3 f/s), the same authors found that decreasing frequencies had the strongest provocative effect.

On the basis of the experience gained in photo-metrazol activation (7), Gastaut and Corriol (8) used double flashes and found that this form of stimulation was very effective when a delay of 50–70 msec. was used.

In 1949, Walter and Shipton (13) described a special technique in which an electronic trigger mechanism made it possible to synchronize the flash of the photic stimulator with various components of the EEG. In 1952, Turton (12) found that the electronic trigger method made 26 out of 120 EEG's from known epileptics, whose routine EEG's showed no specific changes, diagnostic of epilepsy, while the same only happened in 15 cases with ordinary photic stimulation.

MATERIAL AND METHOD

The present case material comprised 1366 patients who were admitted to this hospital for investigation. About 90 per cent of the patients were admitted to the Department of Neurology and the Department of Neurosurgery. It should be noted that the series comprised a large number of mild cases, since many of the patients were admitted after one or a few uncharacteristic seizures. Only patients in whom epilepsy was suspected were subjected to photic stimulation.

The patients were divided into three groups according to the diagnosis:

1. *Symptomatic epilepsy*, *i.e.*, patients in whom an epileptogenic lesion was revealed or could reasonably be suspected to be present.

2. *Cryptogenic epilepsy*, *i.e.*, patients in whom the past history and physical examination did not reveal signs of any epileptogenic lesion.

3. *Suspected epilepsy*, in which it was not possible with certainty to classify the patients as epileptics. This group included many questionable cases, *e.g.*, patients who had had only one uncharacteristic seizure.

As the distinction between cryptogenic and symptomatic epilepsy is of fundamental importance in this paper the criteria applied will be described briefly.

A positive family history was considered a point in favor of cryptogenic epilepsy, at the same time taking notice of the fact that also in symptomatic cases a greater family incidence will be found than in a normal material.

The age of the patients at onset of disease has been given some weight. Thus onset at the age of five to 20 years was considered characteristic of cryptogenic epilepsy, while onset before or after this age would contribute to a diagnosis of symptomatic epilepsy.

In each case the possible significance of birth trauma, craniocerebral injury or infectious disease with cerebral symptoms was evaluated.

A case was classified as symptomatic if neurological examination, X-ray of skull, air-encephalography or arteriography showed pertinent abnormality, or if routine EEG showed focal signs.

Of the seizure types only petit mal was considered indicative of cryptogenic epilepsy. Four cases of petit mal, though, were classified as symptomatic because of relevant abnormal findings on further investigation.

Cases with auras, ictal phenomena, postparoxysmal abnormalities or interseizure symptoms indicating a lesion of a specific cortical area were all classified as symptomatic.

Other seizure patterns were given no weight in the differential diagnosis. Grand mal and the seizures grouped under the heading "uncharacteristic" comprising a variety of minor epileptic manifestations such as short tonic fits, short lapses of conscious-

TABLE 1
Survey of Patients Studied

Diagnosis	N
Cryptogenic epilepsy	445
Symptomatic epilepsy	356
Suspected epilepsy	565
Total	1366

ness with and without the passing of urine or biting the tongue were all classified according to the results of thorough investigation.

Some of the patients were subjected to photic stimulation more than once, but only the result of the first examination is included in this analysis. Since the object of the present study was to assess the value of photic stimulation in the diagnosis of epilepsy, only patients whose routine EEG did not reveal paroxysmal abnormalities are included in the analysis.

Medical antiepileptic treatment was not interrupted before the examination in 37 patients, *i.e.* two per cent, while this treatment had been stopped only 24 hours previously in many patients.

EEG was performed with 8-channel Kaiser electroencephalographs, always with both monopolar and bipolar leads. The 21 electrodes were placed according to the system outlined by Jasper and Kershman, which is described, for example, in Schwab, *Electroencephalography* (1951).

The photic activation was performed with a Kaiser photic stimulator. The light source was a Xenon lamp giving a bluish white light, the composition of which does not deviate much from sunlight. The apparatus is provided with a diffusing screen of a diameter of 16 cm. The light intensity may be varied in three steps. The flash duration is about 300, 200 and 150 microseconds at high, medium and low intensity respectively. The flicker frequency may be varied from 0 to 90 f/s, the intensity falling evenly with increasing frequency. The fall is steepest at the highest intensity. The two highest light intensities can be used only within the frequency range from 0 to 24 f/s, the intensity at a distance of 10 cm being approximately 330,000 and 120,000 foot-candles at the frequency of 4 f/s. At a frequency of 24 f/s the intensity at both adjustments has fallen to about 50,000 foot-candles. At higher flicker frequencies only the lowest light intensity can be used. At this adjustment, the light intensity falls from about 20,000 to 10,000 foot-candles when the flicker frequency is changed from four to 30 f/s. The apparatus incorporates a built-in electronic trigger mechanism rendering it possible to synchronize the flashes with the EEG. Channel 8 of the electroencephalograph was used as the trigger impulse, so that flashes were excited at all positive or negative waves exceeding 5 mm. The flashes were recorded directly on the EEG.

Photic stimulation was performed with exactly the same technique in the entire series. After routine examination, which lasted about 20 minutes, the lamp was placed at a distance of about 10 cm from the closed eyes of the patient. The stimulus frequencies used were 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25 and 30 f/s, each frequency being applied for 35 seconds. At the frequencies from 4 to 22 f/s the medium light intensity was first used for 25 seconds; then the highest intensity was suddenly turned on and used for 10 seconds. At the frequencies of 25 and 30 f/s only the lowest intensity was used. Then stimulation for four minutes was applied with the use of the electronic trigger (ETM) with a lead from the left occipital region to the left ear as the trigger impulse, first for two minutes with the negative and then for the next two minutes with the positive waves as the trigger. Photic stimulation lasted for about 10 minutes. It was not intended to provoke clinical seizures; accordingly, stimulation was interrupted when a seizure seemed to be approaching.

As already mentioned, the analysis comprised only patients with non-paroxysmal routine EEG's.

The routine EEG's were divided into three groups:

1. *Normal EEG*, by which is understood a curve with pure alpha activity (8–13 c/s). In addition, the group also contains EEG's with a larger or smaller component of low voltage fast activity and up to about 10 per cent slow activity of 6–7 c/s, provided that the latter does not occur focally or with a higher amplitude than the background activity. This group contains the EEG's which were on the verge of abnormal.

2. *Diffusely abnormal EEG, i.e.*, with diffuse slow activity below 6 c/s or more than about 10 per cent 6–7 c/s activity.

3. *Focal EEG, i.e.*, with focal slow activity below 8 c/s.

The curves obtained in patients under 15 years of age were assessed in accordance with Gibbs and Gibbs, *Atlas of Electroencephalography* (1950).

The result of photic stimulation was considered to be positive only when paroxysmal abnormalities were excited. These were classified into three categories:

a. *Spike-and-wave discharges* (2½–3½ c/s, regular, bilaterally synchronous).

b. *Other bilateral discharges* (paroxysmal low frequency activity with a high amplitude, distinctly contrasting with the background rhythm, often with an irregular spike component).

c. *Focal spikes* (or sharp waves).

The lowest flicker frequency exciting paroxysmal activity is designated as the activating frequency.

RESULTS

The results obtained in the entire series are presented in Tables 2 and 3.

Among the 1366 patients with unquestionable or suspected epilepsy and non-paroxysmal routine EEG's, photic stimulation excited paroxysmal activity in 150 cases (11.2 per cent).

In patients with normal EEG's, positive results were obtained only in 5.8 per cent of the cases, while the groups with diffusely and focally abnormal routine EEG's showed

TABLE 2

Paroxysmal Activity Evoked by Photic Stimulation in 1366 Patients with Definite or Suspected Epilepsy (Distributed According to Routine EEG)

Routine EEG	Males		Females		Total	
	N	Activated	N	Activated	N	Activated
Normal	324	13 (4.0%)	241	20 (8.3%)	565	33 (5.8%)
Diffusely abn.	374	45 (12.0%)	359	65 (18.1%)	733	110 (15.0%)
Focal	37	4 (10.8%)	31	3 (9.7%)	68	7 (10.3%)
Total	735	62 (8.4%)	631	88 (13.9%)	1366	150 (11.2%)

TABLE 3

Paroxysmal Activity Evoked by Photic Stimulation in 1336 Patients with Definite or Suspected Epilepsy (Distributed According to Age)

Age in years	Males		Females		Total	
	N	Activated	N	Activated	N	Activated
0–5	44	8 (18.2%)	23	7 (30.4%)	67	15 (22.4%)
6–15	150	18 (12.0%)	126	24 (19.0%)	276	42 (15.2%)
16–60	518	36 (6.9%)	464	57 (12.3%)	982	93 (9.5%)
60+	23	0	18	0	41	0
Total	735	62 (8.4%)	631	88 (13.9%)	1336	150 (11.2%)

TABLE 4

Paroxysmal Activity Evoked in 445 Patients with Cryptogenic Epilepsy (Distributed According to Seizure Type)

Seizure type	Males		Females		Total	
	N	Activated	N	Activated	N	Activated
Grand mal	144	22 (15.3%)	126	37 (29.4%)	270	59 (21.9%)
Petit mal	14	3 (21.4%)	14	6 (42.9%)	28	9 (32.1%)
Grand mal and petit mal	26	7 (26.9%)	36	9 (25.0%)	62	16 (25.8%)
Uncharacteristic seizures	39	12 (30.8%)	46	14 (30.4%)	85	26 (30.6%)
Total	223	44 (19.7%)	222	66 (29.7%)	445	110 (24.7%)

TABLE 5

Paroxysmal Activity Evoked in 445 Patients with Cryptogenic Epilepsy (Distributed According to Age)

Age in years	Males		Females	
	N	Activated	N	Activated
0–15	95	20 (21.1%)	84	27 (32.1%)
16–60	127	24 (18.9%)	138	39 (28.3%)
60+	1	0	0	0
Total	223	44 (19.7%)	222	66 (29.7%)

TABLE 6

Paroxysmal Activity Evoked in 445 Patients with Cryptogenic Epilepsy (Distributed According to Routine EEG)

Routine EEG	Males		Females	
	N	Activated	N	Activated
Normal	83	9 (10.8%)	70	16 (22.9%)
Diffusely abnormal	140	35 (25.0%)	152	50 (32.9%)
Total	223	44 (19.7%)	222	66 (29.7%)

activation in 15.0 and 10.3 per cent respectively.

As shown in Table 3, the effectivity of photic stimulation was highest in the youngest age groups and decreased gradually with advancing age. Paroxysmal activity was not excited in any of the patients in the group over 60 years of age.

Both in the groups with normal and diffusely abnormal routine EEG's and in all age groups, females revealed activation more frequently than males. In the entire series, paroxysmal activity was provoked in 8.4 per cent of the males and in 13.9 per cent of the females. This difference is statistically significant.

In order to throw further light on the conditions observed, the results obtained in the two diagnostic groups comprising cryptogenic and symptomatic epilepsy are given in Tables 4 to 9.

It appears that photic stimulation was much more effective in cryptogenic epilepsy,

TABLE 7

Paroxysmal Activity Evoked in 356 Patients with Symptomatic Epilepsy (Distributed According to Seizure Type)

Seizure type	Males		Females		Total	
	N	Activated	N	Activated	N	Activated
Grand mal	96	7 (7.3%)	53	1 (1.9%)	149	8 (5.4%)
Petit mal	2	1	2	0	4	1 —
Focal seizures	56	1 (1.8%)	26	2 (7.7%)	82	3 (3.7%)
Temporal lobe seizures	24	3 (12.5%)	22	3 (13.7%)	46	6 (13.0%)
Uncharacteristic seizures	42	3 (7.1%)	33	3 (9.1%)	75	6 (8.0%)
Total	220	15 (6.8%)	136	9 (6.6%)	356	24 (6.7%)

activation being observed in 19.7 per cent of the males and 29.7 per cent of the females; the corresponding figures for symptomatic epilepsy were 6.8 and 6.6 per cent respectively.

The aforementioned difference in the response of males and females to photic stimulation was seen only in cryptogenic epilepsy, and this difference was revealed both in cases with normal and diffusely abnormal routine EEG's and in all age groups.

In Table 4, the results of photic stimulation are related to the seizure types within the group of cryptogenic epilepsy. Only the grand mal group is sufficiently large to allow of a definite evaluation. Here, there is a distinct preponderance of positive responses in females, *viz.* in 29.4 per cent of the cases as compared with 15.4 per cent in males. The corresponding results for symptomatic epilepsy are shown in Table 7. In this group of grand mal epilepsy, the conditions are reversed, activation being found in 7.3 per cent among males and in only 1.9 per cent among females. However, this difference is not statistically significant.

In both diagnostic groups, the activation was found to decrease with advancing age. As in the entire series, the lowest incidence of positive results was obtained in the groups with normal routine EEG's. In the group of symptomatic epilepsy, patients with focal abnormalities in the routine EEG's were more sensitive to photic stimulation than patients with diffusely abnormal EEG's (Table 9). The difference is not statistically significant.

The results obtained in the group of suspected epilepsy appear in Table 10. Positive results were also predominant among females in this group, but as this diagnostic group is very heterogeneous, no definite conclusions can be drawn from these figures.

Table 11 presents the types of the excited paroxysms. Only in five cases did photic stimulation result in focal spikes or sharp waves. In 27 cases, typical 2½–3½ c/s bilaterally synchronous spike-and-wave discharges were provoked; of these, 26 belonged to the group of cryptogenic epilepsy. The spikes and waves provoked differed

TABLE 8

Paroxysmal Activity Evoked in 356 Patients with Symptomatic Epilepsy (Distributed According to Age)

Age in years	Males		Females	
	N	Activated	N	Activated
0–15	32	3 (9.4%)	22	2 (9.1%)
16–60	176	12 (6.8%)	105	7 (6.7%)
60+	12	0	9	0
Total	220	15 (6.8%)	136	9 (6.6%)

TABLE 9

Paroxysmal Activity Evoked in 336 Patients with Symptomatic Epilepsy (Distributed According to Routine EEG)

Routine EEG	Males		Females	
	N	Activated	N	Activated
Normal	71	3 (4.2%)	44	2 (4.5%)
Diffusely abn.	116	8 (6.9%)	69	5 (7.2%)
Focal	33	4 (12.1%)	23	2 (8.7%)
Total	220	15 (6.8%)	136	9 (6.6%)

TABLE 10

Paroxysmal Activity Evoked in 565 Patients with Suspected Epilepsy

Age in years	Males		Females		Total	
	N	Activated	N	Activated	N	Activated
0–15	67	3	43	2	110	5
16–60	215	0	221	11	436	11
60+	10	0	9	0	19	0
Total	292	3 (1.0%)	273	13 (4.8%)	565	16 (2.8%)

TABLE 11

Classification of the Evoked Paroxystic Activity According to Diagnosis

	Spike-and-wave	Other bilateral	Focal
Cryptogenic epilepsy	26	84	0
Symptomatic epilepsy	1	19	4
Suspected epilepsy	0	15	1
Total	27	118	5

from those occurring spontaneously in that they usually came on in short series with a duration of 1–3 seconds and were unaccompanied by seizures. Only in a few cases were series of a longer duration, accompanied by absence, provoked. The most common finding in all three diagnostic groups was irregular, bilateral paroxysmal activity.

Figures 1 and 2, reporting data from all activated patients, show the distribution according to the lowest activation flicker frequency. The last column in the diagrams shows the number of cases in which paroxysmal activity was excited by electronic trigger when ordinary photic stimulation had proved ineffective.

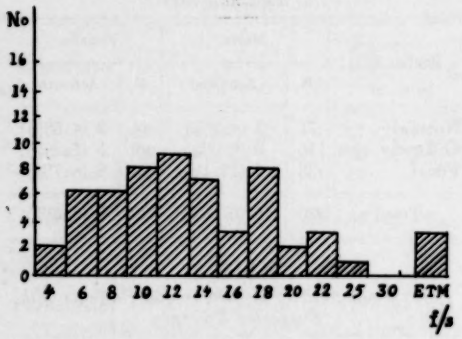


FIG. 1. Fifty-eight patients (0–15 years) distributed according to the lowest activating flicker frequency. The last column shows the patients who were activated only by means of electronic trigger (ETM).

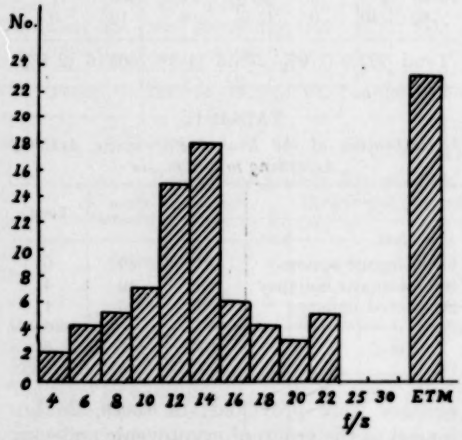


FIG. 2. Ninety-two patients (16–60 years) distributed as in Figure 1.

In the age group from 16 to 60 years, positive results show a distinct peak at the frequencies of 12 and 14 f/s. The age group from 0 to 15 years shows greater dispersion of the lowest activating frequencies within the range from 6 to 18 f/s. The low frequencies (4, 6 and 8 f/s) were, relatively, a little more effective in the younger than in the older age group. Paroxysmal activity exclusively excited by ETM was seen in 23 cases in the group from 16 to 60 years, but only in three cases in the group from 0 to 15 years.

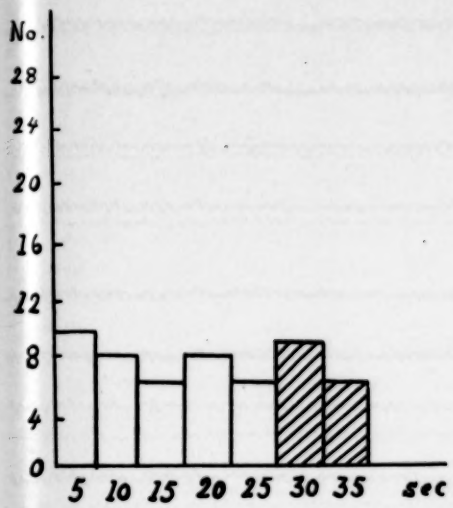
As already mentioned, each flicker frequency was used for 35 seconds. At the frequencies 4 to 22 f/s, the stimuli were applied with the medium light intensity for 25 seconds, followed by a sudden change to the highest intensity, which was applied for 10 seconds.

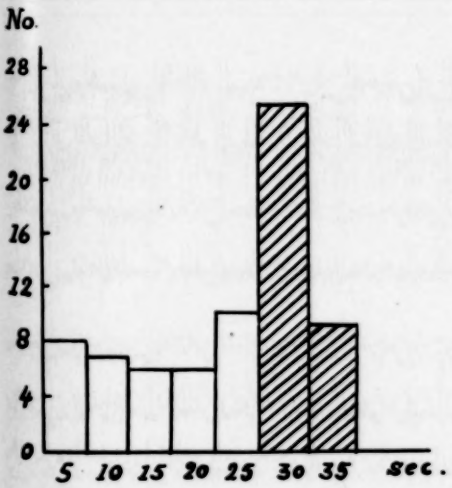
In Figures 3 and 4, which reflect all activated patients except those who responded to ETM only, the patients with positive response are grouped according to the length of time (0–35 sec.) the lowest activating frequency was applied before paroxysmal activity occurred. Positive responses are fairly evenly distributed over the first 25 seconds both in males and females. In females, the sudden increase in the light intensity after the lapse of 25 seconds provoked a markedly increased number of paroxysmal responses during the first five seconds after the change, but during the next five seconds the number of new paroxysmal responses fell to the same level as before the increase in the light intensity. In males, no changes which could be ascribed to the increased light intensity were observed.

So far, only the actual paroxysmal responses have been considered. Two other conspicuous and characteristic reactions to photic stimulation are described below.

These reactions were:

1. A photomyoclonic response evidenced by the development of facial or generalized





FIGS. 3 (Males) and 4 (Females). Duration of stimulation (in sec.) with the lowest activating frequency before activation occurred. The light intensity was increased after the lapse of 25 seconds. (Patients activated only by means of ETM are not included.)

myoclonic jerks during photic stimulation. This response was accompanied by a spike-like activity, which was usually first seen in the frontal leads and often showed distinct recruitment. The spikes are presumably of muscular origin. This response occurred nearly always or was most pronounced when the highest light intensity was used in the stimulation, and ceased at once when photic stimulation was interrupted; it never developed into characteristic epileptic seizures, and no accompanying change in the level of consciousness could be demonstrated. As appears from Table 12, this response was fairly rare, but occurred with almost the same frequency in the three diagnostic groups.

TABLE 12

Non-Paroxysmal Reactions

	N	Photomyoclonic reaction	Irregular activity with low-voltage spikes
Suspected epilepsy	565	3 (0.5%)	19 (3.4%)
Symptomatic epilepsy	357	3 (0.8%)	9 (2.5%)
Cryptogenic epilepsy	445	3 (0.7%)	7 (1.6%)

2. Another response to photic stimulation, which was slightly more common, was diffuse, continuous irregularities in the form of rapidly changing frequencies, irregular slow activity and low spikes. There were no recruitment or any myoclonic jerks, but the patients often complained of marked discomfort in the form of dizziness and a feeling as if they were going to faint, but actual syncopal attacks or typical manifestations of seizures did not occur. This response would often continue for several minutes, but like the photomyoclonic response it ceased as soon as photic stimulation was interrupted. As shown in Table 12, phenomena of this type were most frequent in the group of suspected epilepsy and rarest in the group of cryptogenic epilepsy, but the difference was not statistically significant.

These reactions were observed in 44 patients (12 males and 32 females). None of these was under 15 years of age, 40 were between 16 and 60, and four patients were over 60 years of age.

DISCUSSION

As a method of provocation, photic stimulation offers several advantages. The vari-

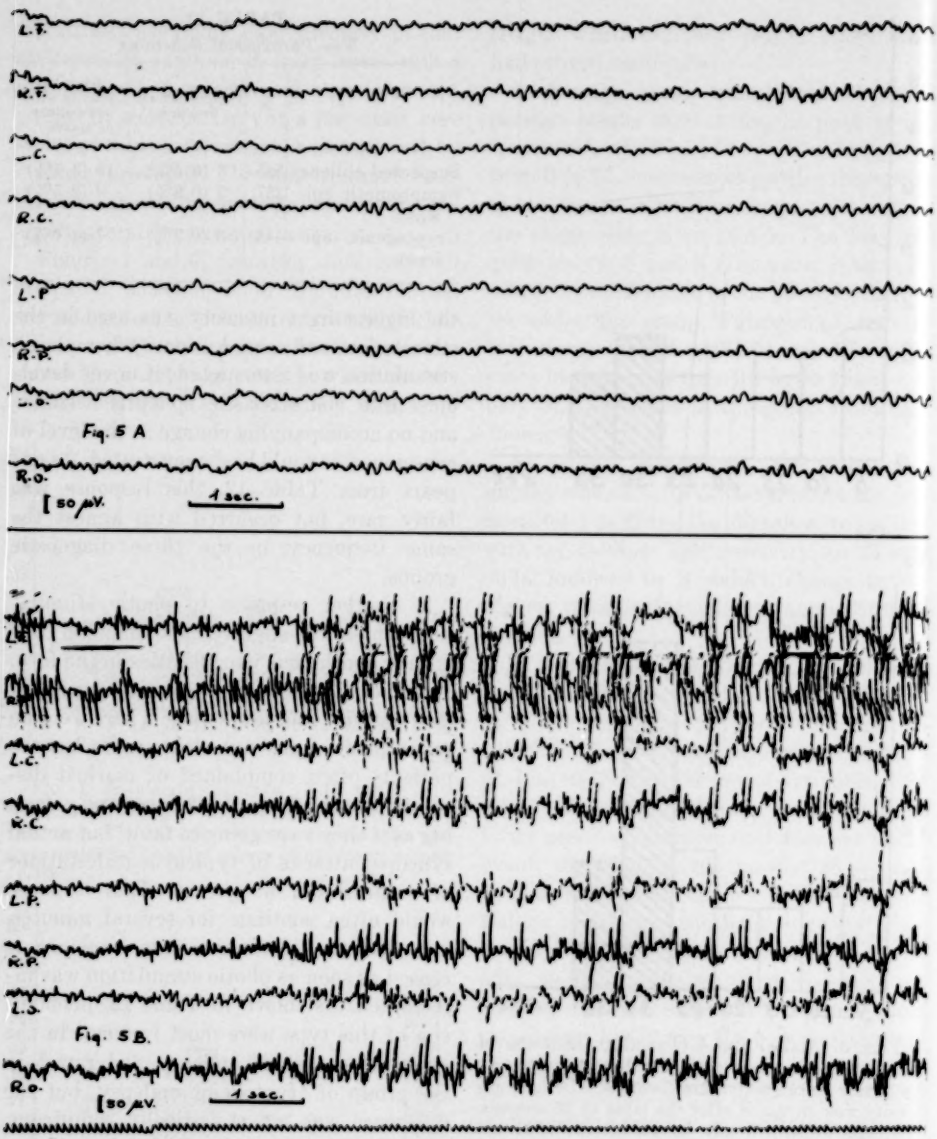


FIG. 5. Female patient, aged 43 years; cryptogenic epilepsy. A: Routine EEG classified as normal. B: Photomyoclonic response during photic stimulation.

ous phases of the stimulation are reproducible; the method can be used even in children and other less co-operative patients, and it is usually not associated with any discomfort. In most cases, unwanted seizures can be avoided. In the present series, only seven seizures of grand mal or psychomotor type occurred.

The diagnostic value of a method of provocation depends not only on its effectiveness but just as much on its specificity. The present study does not elucidate the

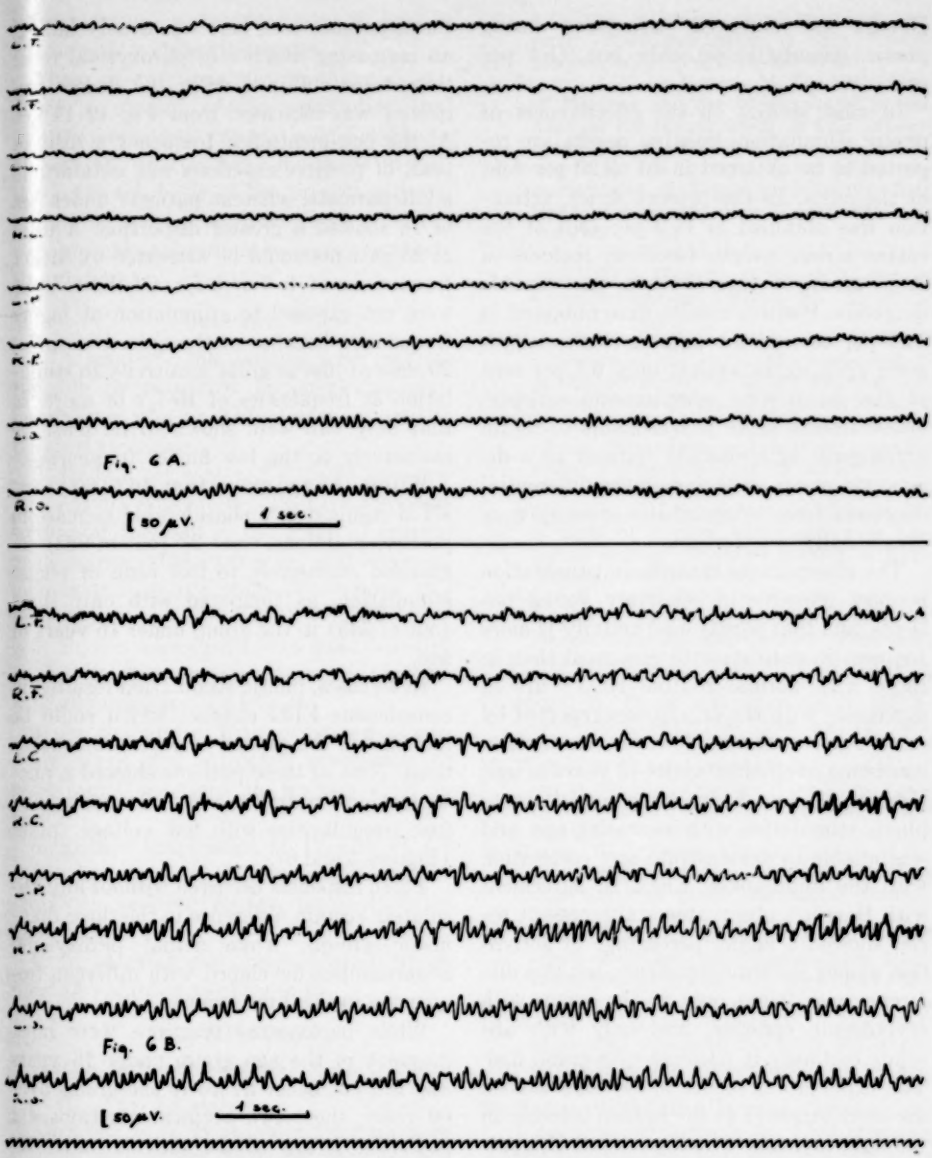


FIG. 6. Female patient, aged 49 years; cryptogenic epilepsy. A: Routine EEG classified as normal. B: Diffuse irregular activity with small spikes during photic stimulation.

specificity of the method, since the series does not contain any controls. Walter (16) stated that paroxysmal response to photic stimulation occurs in two per cent of normal individuals. In a series of air-force applicants without signs of organic nervous disease and with normal routine EEG's, Buchthal and Lennox (4) provoked paroxysmal activity by photic stimulation in 1.4 per cent. In a series of 70 normal children,

Herrlin (9) observed paroxysms during photic stimulation in only one (1.4 per cent).

In most studies on the effectiveness of photic stimulation, positive results are reported to be obtained in 10 to 20 per cent of the cases. In the present series, activation was obtained in 11.2 per cent of the entire series, which, however, includes a large group of cases with a questionable diagnosis. Positive results were obtained in 24.7 per cent of the patients with cryptogenic epilepsy as against only 6.7 per cent of the group with symptomatic epilepsy. These results make it reasonable to retain cryptogenic or idiopathic epilepsy as a diagnostic group, even though the differential diagnosis from symptomatic epilepsy may occasionally be uncertain.

The observations that photic stimulation is most effective in relatively young patients, and that paroxysmal activity is more frequent in patients with abnormal than in those with normal routine EEG's are in agreement with the experiences reported by most other authors. However, in a series consisting of children under 15 years of age, Herrlin (9) found increasing sensitivity to photic stimulation with increasing age, and was unable to demonstrate any correlation with the unprovoked EEG. In agreement with Herrlin's observations, the present series showed a higher percentage of activation among the female patients, but this difference was found only in the group with cryptogenic epilepsy, and only with absolute certainty in patients with grand mal. The explanation seems to be that women are more sensitive to the sudden increase in the light intensity which was used (Figures 3 and 4).

In spite of differences in equipment and technique, the various investigators arrive at largely consistent results. Accordingly, the technique used does not seem to be of decisive importance. Flicker frequency apparently plays a greater role than light intensity. Although the light intensity with the apparatus used here was evenly falling, an increasing number of paroxysmal reactions were obtained when the flicker frequency was increased from 4 to 12–14 f/s. At the last-mentioned frequency a distinct peak of positive reactions was obtained in adult patients, whereas patients under age of 16 showed a greater dispersion. A total of 25 patients could be activated by flicker frequencies of 4, 6 or 8 f/s. Of these, three were not exposed to stimulation at higher frequencies because of threatened seizures; 20 showed just as great sensitivity to stimulation at frequencies of 10 f/s or more, so that only two were shown to be sensitive exclusively to the low flicker frequencies.

Within the age group from 16 to 60 years, ETM resulted in a considerable increase in positive reactions, since 23 (out of 982) responded exclusively to this form of photic stimulation, as compared with only three (out of 343) in the group under 16 years of age.

In 44 cases, photic stimulation resulted in conspicuous EEG changes which could be included in the groups of paroxysmal reactions. Nine of these patients showed a photomyoclonic response, while 35 revealed diffuse irregularities with low voltage spikes (Figures 5 and 6).

These responses occurred without any absolutely certain difference in the three diagnostic groups, while actual paroxysmal abnormalities developed with different frequencies in the three groups.

While paroxysmal reactions were most frequent in the age group under 16 years and did not occur at all in the group over 60 years, these two atypical reactions did not occur in any of the patients under 16, but in 40 cases in the group from 16 to 60 years, and in four in the group over 60. The age distribution of the patients who showed these reactions thus differed from that observed in the patients who responded with typical paroxysmal activity.

Finally, it must be mentioned that even when photic stimulation was continued,

these reactions were never seen to lead to characteristic epileptic seizures.

These observations may be taken as evidence in support of the assumption that these two reactions must be considered to be non-specific in the EEG diagnosis of epilepsy. On the basis of the present series it cannot be decided whether these reactions were normal or abnormal responses to photic stimulatoin.

SUMMARY

1. A total of 1366 patients with unquestionable or suspected epilepsy and non-paroxysmal routine EEG's were exposed to photic stimulation.

2. In 11.2 per cent of the cases paroxysmal activity was excited. Positive responses were most frequent in the group of cryptogenic epilepsy (24.7 per cent) and less common in that of symptomatic epilepsy (6.7 per cent).

3. Photic stimulation was most effective in the younger age groups and in patients with abnormal routine EEG's.

4. In the group with cryptogenic epilepsy there was a higher proportion of paroxysmal reactions in females than in males.

5. Flicker frequencies of 12 and 14 f/s were most effective. ETM resulted in an increase in positive results, particularly in adult patients.

6. In 44 cases, responses occurred which must be regarded as nonspecific.

REFERENCES

1. Adrian, E. D. and Matthews, B. H. C. Potential changes from the occipital lobes in man. Brain, **57**: 355–385, 1934.
2. Bickford, R. G. et al. Some observations on the mechanism of photic and photo-metrazol activation. Electroencephalog. & Clin. Neurophysiol., **4**: 219–222, 1952.
3. Brazier, M. A. A review of physiological mechanisms of the visual system in relation to activating techniques in electroencephalography. Electroencephalog. & Clin. Neurophysiol., Suppl. No. **4**: 93–107, 1953.
4. Buchthal, F. and Lennox, M. The EEG effect of Metrazol and photic stimulation in 682 normals. Electroencephalog. & Clin. Neurophysiol., **5**: 545–558, 1953.
5. Gastaut, H. and Gastaut, Y. Les formes experimentales de l'epilepsie humaine: Epilepsie photogenique. Rev. Neurol. **80**: 161–182, 1948.
6. Gastaut, H. Effets des stimulation physiques sur l'EEG de l'homme. Electroencephalog. & Clin. Neurophysiol., Suppl. No. **2**: 69–82, 1949.
7. Gastaut, H. Combined photic and Metrazol activation of the brain. Electroencephalog. & Clin. Neurophysiol., **2**: 249–261, 1950.
8. Gastaut, H. and Corriol, J. Note preliminaire sur un procede nouveau et particulierement efficace de stimulation lumineuse intermittente. Electroencephalog. & Clin. Neurophysiol., **3**: 87–88, 1951.
9. Herrlin, N. K. EEG with photic stimulation: A study of children with manifest or suspected epilepsy. Electroencephalog. & Clin. Neurophysiol., **6**: 573–589, 1954.
10. Laget, P. and Humbert, R. Facteurs influcant la réponse electroencephalographique a la photostimulation chez l'enfant. Electroencephalog. & Clin. Neurophysiol., **6**: 591–597, 1954.
11. Melin, K. Photic stimulation as an aid in electroencephalography. Acta pædiat., **39**: 148–157, 1950.
12. Turton, E. C. An electronic trigger used to assist in the EEG diagnosis of epilepsy. Electroencephalog. & Clin. Neurophysiol., **1**: 83–91, 1952.
13. Walter, W. G., Dovey, V. J. and Shipton, H. V. Analysis of the electrical response of the human cortex to photic stimulation. Nature, **158**: 541–542, 1946.
14. Walter, W. G. and Walter, V. J. The central effects of rhythmic sensory stimulation. Electroencephalog. & Clin. Neurophysiol., **1**: 57–86, 1949.
15. Walter, W. G. and Walter, V. J. The effect of physical stimuli on the EEG. Electroencephalog. & Clin. Neurophysiol., Suppl. No. **2**: 60–68, 1949.
16. Walter, W. G., Hill, D. et al. Discussion on the recent advances in the EEG diagnosis of epilepsy. Proc. Roy. Soc. Med. **44**: 315–332, 1951.
17. Weil, A. A. Non-sleep activation of electroencephalogram. Dis. Nerv. Syst., **13**: 11–16, 1952.

STUDIES ON HUMAN SALIVA: A TYRAMINE-LIKE COMPONENT AND ITS RESPONSE TO AUTONOMIC STIMULATION[1]

VICTOR SCHENKER, PH.D.[2] AND ANNE C. SCHENKER, B.SC.

Salivary function is known to be controlled essentially by the autonomic nervous system. Thus mediated, the secretory activity of the salivary glands provides a measurable index of autonomic function. The importance of this to the study of emotional disorders and psychosomatic diseases is clear. Most studies in humans which have made use of this relationship have been confined to measurement of flow volume. Strongin and Hinsie (10) measured parotid flow in chronic schizophrenics. In a preliminary study, these investigators reported a seven-fold higher rate in these patients over that of healthy control subjects. Lourie (7) showed that in early childhood the parotid flow is characteristically 5 to 6 times higher than that eventually attained post-puberally and in adulthood. The high rate in early life was attributed to the undeveloped inhibitory influence of higher centers over the parasympathetic division of the central nervous system. From such data, salivary function, in terms of parotid flow, would appear to reflect *in some measure* the relative degree of integration between higher centers and the autonomic nervous system. Since comparatively little is known about the changes in biochemical constitution of the saliva in humans under these and other experimental conditions, further study of chemical salivary changes concomitant with changes in autonomic activity are indicated.

Salivary components and their relation to autonomic function have been relatively widely studied in animals, mainly in the cat. Vasoactive substances which vary in activity with autonomic stimulation have been described (1, 6). Particularly relevant to our experiments is the early report of Cattell, Wolff and Clark (2) who described the liberation from the submaxillary gland of the cat, of a neurohumoral agent having the properties of "adrenin"; and the more recent experiments of Strömblad (9) which demonstrate in these glands the presence of a monoamine oxidase acting upon tyramine substrate. Severing the autonomic nerves to the gland was followed by changes in activity of this enzyme.

Recent studies on the neurohumoral aspects of emotional disorders have placed much emphasis upon the role of biogenic amines and related compounds in connection with autonomic nervous system function. With the availability of sensitive fluorescence techniques for the detection of microgram quantities of such compounds, we were prompted to explore 1) the possibility of the presence of amines in human mixed saliva, and 2) if found present, whether autonomic stimulation produced any consistent changes in their concentration. This report describes preliminary experiments studying this aspect of salivary function in man.

DETECTION AND CHARACTERIZATION OF SALIVARY FLUOROPHORE

Experiments were done initially in six healthy male members of the laboratory staff. Mixed saliva was collected in the morning with the subjects either in the

[1] This paper was presented in part at the 115th Meeting of the Research Society, State University of New York, Downstate Medical Center, January, 1958.

[2] Biochemical Research Section, Department of Psychiatry, State University of New York, Downstate Medical Center, Brooklyn, New York. The authors acknowledge with thanks the participation in some of the experiments reported of Mr. Joseph Zuch and Mr. Stanley Wissner, who volunteered their services as laboratory assistants during the summer months of 1958.

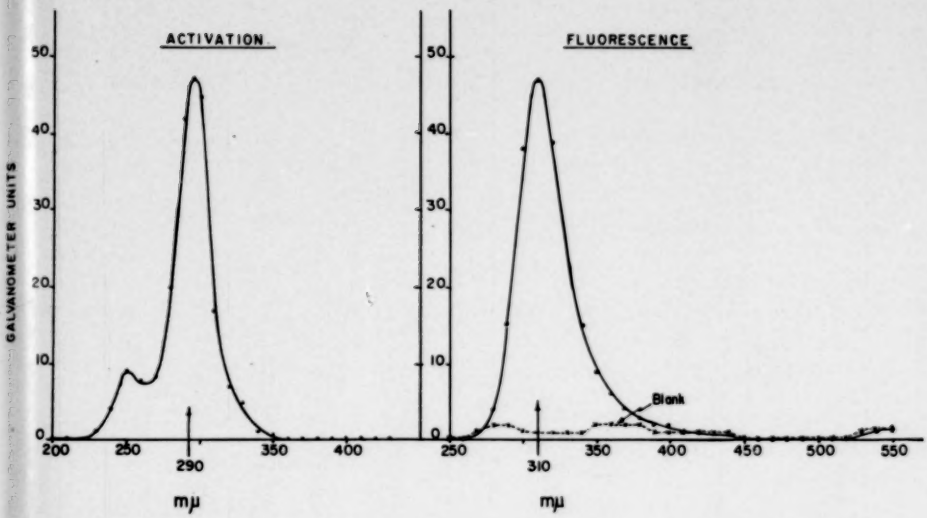


FIG. 1. Activation and fluorescence spectra of the salivary component extracted from human mixed saliva. Maximum activity: 290 mμ, maximum fluorescence: 310 mμ.

fasting state or several hours after the last intake of food. Prior to collection, the mouth was carefully cleansed by gargling and rinsing with warm water followed by distilled water. The saliva secreted during five minutes after washing was discarded. This procedure was adopted and routinely applied in all subsequent experiments. In most instances salivary secretion was stimulated by passive chewing of paraffin wax. Aliquots of 5 to 10 ml. of whole saliva were collected and extracted according to Udenfriend, Weissbach and Clark (11) into two to three volumes of n-butanol from salt saturated solution at pH 10. After several washings with buffer, the butanol extracts were shaken with heptane and 0.1 N HCl. The acid fractions were then separated and scanned for maximum activation and fluorescence using the Aminco-Bowman spectrophotofluorometer.

RESULTS

In all cases there occurred a marked fluorescence peak at 310 mμ, maximal at activation of 290 mμ as shown in Figure 1. This spectral pattern was consistently found on numerous occasions when repeated in these subjects. Identical patterns were likewise found when the procedure was carried out in 29 hospital patients (27 rehabilitated alcoholics, one case of obesity with cardiac involvement and one case of acute pancreatitis). It thus became apparent that human saliva contains, in amounts varying from one individual to another, a fluorophore with definite and consistent fluorescence characteristics.

Perusal of published spectral data (3) for various biological compounds disclosed that the characteristics of the salivary fluorophore corresponded to those of tyrosine and/or tyramine.[3] Tyrosine, however, was unequivocally eliminated when it was found empirically that this compound—which is a constituent of human saliva—is removed by the extraction procedure here employed. Furthermore, it was established that the pH for maximal fluorescence of salivary extracts (pH 5.2–5.6) corresponds to that

[3] Duggan *et al.* (3) report activation for these compounds at 275 mμ. The difference between this value and that found above is attributable to the variation among individual instruments (8).

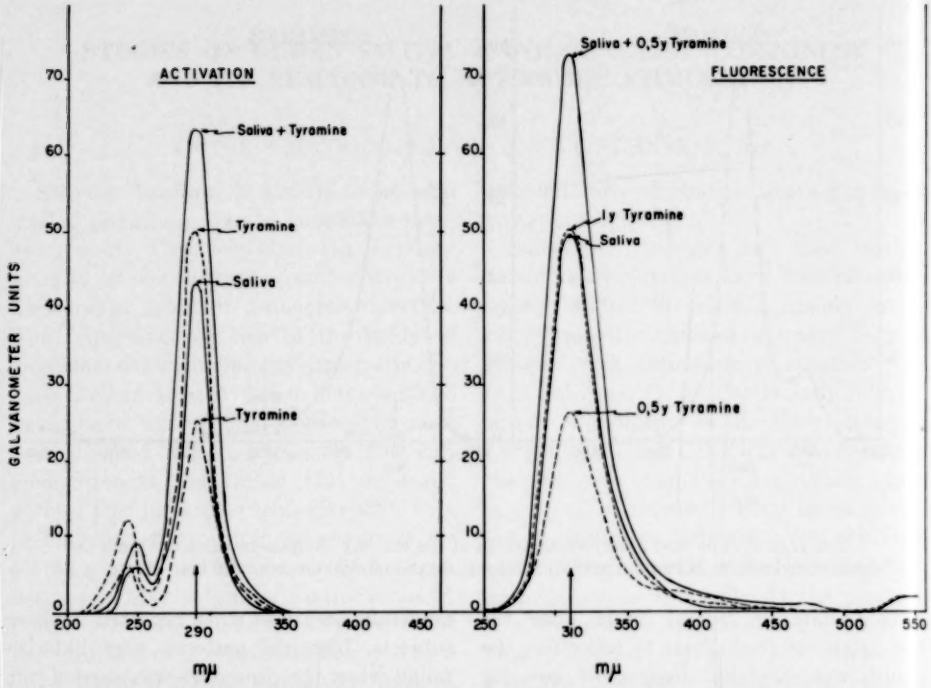


FIG. 2. Comparative activation and fluorescence spectra of tyramine, saliva and saliva with added tyramine identically extracted. Note the similarity of spectral characteristics between the salivary component and authentic tyramine.

of tyramine similarly extracted, rather than to that of tyrosine. In Figure 2 are shown spectral patterns for extracts of saliva, of authentic tyramine hydrochloride,[4] and of saliva with added tyramine. It is seen that the curves are identical in character both as to activation and fluorescence, the saliva in this instance containing an equivalent of 1 μg tyramine/ml. Similar correspondence in spectra was found in the case of nitrosonaphthol HNO_3 derivatives prepared from extracts of saliva and of tyramine according to Waalkes and Udenfriend (12). Fluorescence curves at maximum activation of 472 mμ are shown in Figure 3.

Pharmacologic characterization of a concentrate of salivary extract was attempted by testing against a 3×10^{-5} M solution of tyramine HCl using the spiral strip preparation of a rabbit aorta sensitized by pre-treatment with iproniazid 2×10^{-3} M (4). The concentrate was prepared from the acid extracts of normal saliva by lyophilization followed by the removal of excess salt from the dry residue by two extractions into "absolute" ethanol. The alcoholic fraction was then taken to dryness under nitrogen in partial vacuum and the dry residue dissolved in water. The fluorescence characteristics of the initial acid extract were retained by the final aqueous fraction. When this extract was tested in the muscle preparation, identical contractions, which were inhibited by 2×10^{-5} M cocaine, were found in the case of the extract as for the tyramine reference standard. No attempt at quantitation was made in this experiment, the sole object being to observe the qualitative

[4] Tyramine Hydrochloride, M.A., Mann Research Laboratories, Inc., N Y.

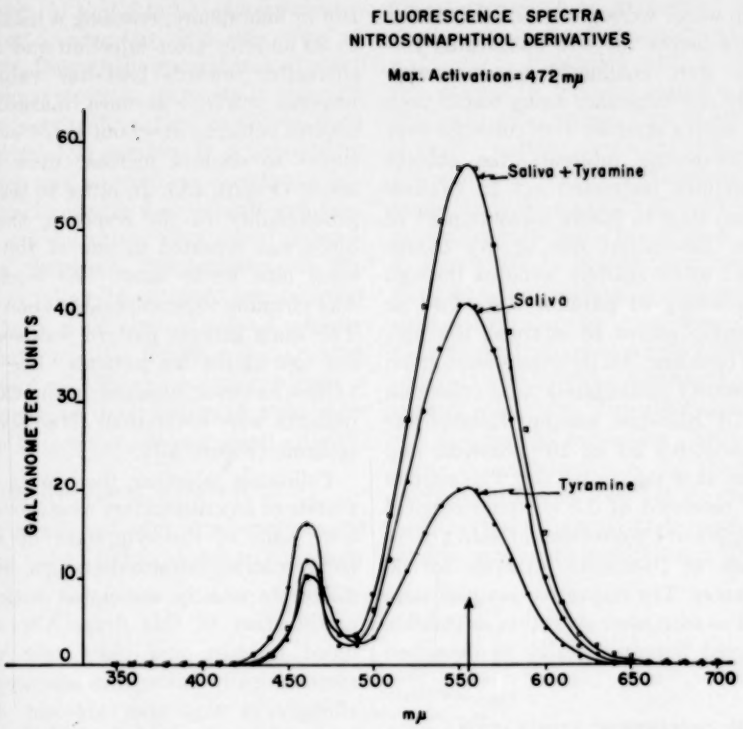


FIG. 3. Fluorescence spectra of nitrosonaphthol-HNO_3 derivatives of tyramine and saliva extracts, singly and in combination. Maximum activation: 472 mμ, maximum fluorescence: 550–560 mμ.

similarity between salivary extract and tyramine. It should be noted that the response described cannot be unequivocally attributed to tyramine specifically; other amines can be present by the extraction procedure employed. The experiment, however, does indicate the presence of an hydroxylated phenyl amine with sympathomimetic activity. Known compounds of this nature (dopamine, norepinephrine, epinephrine) are eliminated from the extract by virtue of the spectral characteristics described above. There is thus good presumptive evidence for the salivary fluorophore in question being tyramine.

EXPERIMENTS USING AUTONOMIC DRUGS

The effect of autonomic stimulation upon the secretion of salivary factor was tested by the injection of urecholine[5] and of epinephrine[6] as the respective cholinergic and adrenergic agents. Twelve subjects were studied, of whom two were healthy young men from the laboratory staff and ten were rehabilitated alcoholics. All twelve subjects received urecholine. Nine (one control and eight patients) were tested with both urecholine and epinephrine. In all cases physiological saline was injected as control. A standardized experimental procedure was followed throughout; subjects were tested in the post-absorptive fasting state in a quiet room, comfortably at bed rest in a semi-recumbent position. In order to avoid the possible effects of thirst, 200 to 300

[5] Bethanechol Chloride, Merck (urethane of B. Methylcholine Chloride).

[6] Adrenaline Chloride, Parke Davis.

ml. of tap water were given to drink about 15 minutes before the test was begun. Experiments were conducted on successive days, only one substance being tested each 24 hours. Saliva samples were collected over exactly 10-minute intervals, the subject being carefully instructed not to swallow any saliva, thus to insure measurement of flow rate. Discomfort due to dry mouth was found to be entirely avoided through passive chewing of paraffin wax. Two or three samples served to establish the pre-injection base line. All injections were given subcutaneously immediately after collection of the last base-line sample. Epinephrine was given at 0.3 ml. of 10^{-3} solution, and urecholine at 4 mg. in 0.8 ml. The control injection consisted of 0.5 ml. physiological saline. Successive collections of saliva were then made at 10-minute intervals for 60 to 70 minutes. The respective samples were extracted as soon after collection as possible and assayed fluorometrically as described above.

EFFECT OF CHOLINERGIC STIMULATION

In contrast to the saline control, injection of urecholine was followed by a definite pattern of changes manifest in a progressive rise in fluorophore, reaching a maximum 20 to 30 minutes after injection and declining thereafter towards base-line values. This response curve was most marked in the control subjects in whom there occurred a three- to six-fold increase over base-line levels (Figure 4A). In order to test the reproducibility of the response, the experiment was repeated in one of the controls some nine weeks later. The second curve was virtually superimposable upon the first. The same general pattern was seen in all but two of the ten patients. The maximal values, however, attained in the case of the patients were lower than those seen in the controls (Figure 4B).

Following injection, there were no complaints of any discomfort whatsoever. There were none of the symptoms of sweating, lachrymation, intestinal cramps, or urge to micturate usually associated with the administration of this drug. Alterations in blood pressure and pulse rate were not systematically followed in all cases, so that changes in this area are not definitely known. However, in the few instances where measurements were made, there was no greater variation seen after injection than before. This is perhaps to be expected since

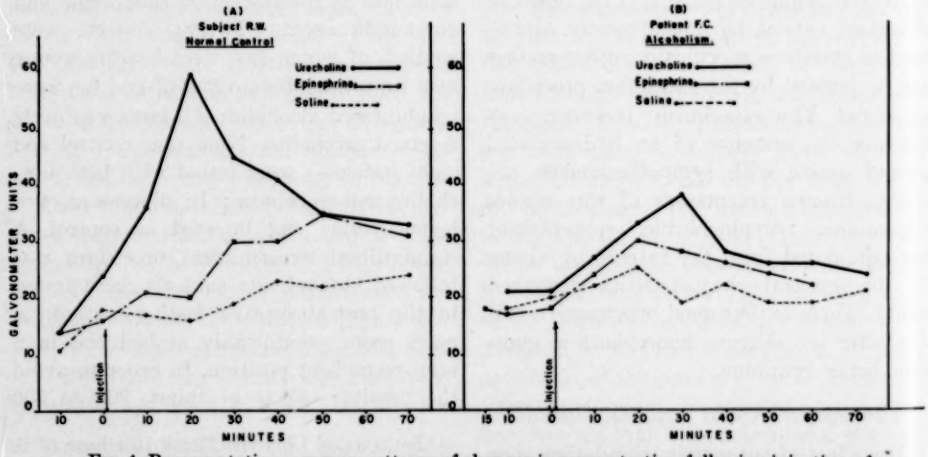


FIG. 4. Representative response patterns of changes in concentration following injection of urecholine, epinephrine and saline in healthy controls (A), and alcoholic patients (B). Concentrations (ordinates) are proportional to galvanometer units.

it is known (5) that a fall in blood pressure occurs but occasionally as a side effect of urecholine. Despite the general lack of other autonomic symptoms, increases in salivary flow rate occurred varying in degree from one individual to another. It is noteworthy that there was no uniform correlation between the changes in flow volume and fluorophore concentration. This would indicate that the increased concentration of the latter seen following autonomic stimulation is not wholly a reflection of rate of salivary flow. There is little doubt, however, that the pattern of changes seen represents a true response to the injection of a cholinergic agent in terms of salivary gland activity.

EFFECT OF ADRENERGIC STIMULATION

The changes in fluorophore concentration following the injection of epinephrine were not as consistent as were those seen after urecholine. As shown in Figure 4A, the normal subject responded with a progressive rise, similar to, but of a higher degree than that seen after saline. One of the patients showed a pattern somewhat similar to this, whereas in six others, fluorophore secretion tended to reach a peak within 20 to 40 minutes after injection, then subside as shown in Figure 4B. In two of these patients, the peak was very marked indeed, with a two- to five-fold increase over base-line levels (Figure 5). Only one patient failed to show any response differing significantly from his control saline test. This individual also did not respond to urecholine. No reason for these inconsistencies is apparent at this early stage. It might be that the dose level of epinephrine used was inadequate, or, what might seem more important in the light of

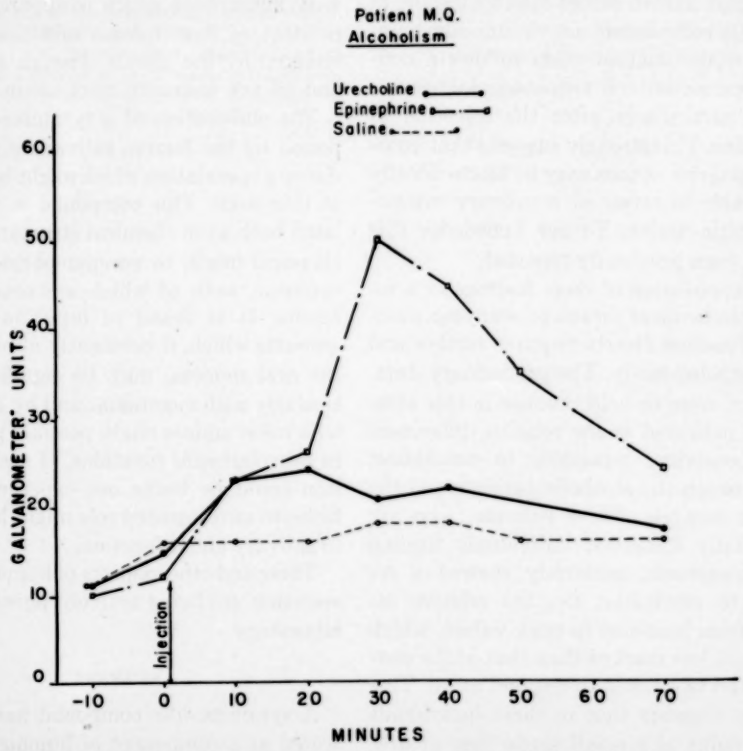


FIG. 5. Response pattern of changes in an alcoholic subject after injection of urecholine, epinephrine and saline showing the marked response to epinephrine in this patient.

the marked responses mentioned, due to a difference in responsivity among individuals to small amounts of epinephrine.

As in the case of stimulation with urecholine, there were no complaints of discomfort or other untoward signs. Changes in salivary flow volume did occur, but varied considerably from one subject to the other. The lack of any correlation between fluorophore concentration and flow volume in these tests was even more marked than those with urecholine. This was particularly evident in the above two patients with the high peak values. In these, the flow volume was actually lower at the high fluorophore levels than those found at pre-injection base-line.

DISCUSSION

These preliminary experiments demonstrate that human mixed saliva contains as one of its components a tyramine-like compound whose concentration follows a definite response pattern with autonomic stimulation, particularly after the injection of urecholine. This strongly suggests that autonomic activity *in man* may be biochemically measurable in terms of a salivary sympathomimetic amine. To our knowledge this has not been previously reported.

The application of these findings as a reliable biochemical means of studying autonomic function clearly requires further and more detailed study. The preliminary data, however, seem to hold promise in this area. This is indicated in the relative differences in responsivity, especially to urecholine, seen between the alcoholic patients and the healthy controls. These patients, who are emotionally disturbed individuals tending to be vagotonic, uniformly showed a response to urecholine, *i.e.*, the relative increase from base-line to peak values, which was much less marked than that of the controlls, and two failed to respond at all. This possibly suggests that in these individuals the stimulus of a small single dose of urecholine was insufficient to elicit a change due to an existing high level of parasympathetic activity. Such an interpretation, however, demands quantitative data on relative resting values in a much larger and varied population than that studied here.

A noteworthy observation was the fact that such marked changes in salivary factor could be elicited by a dose level of urecholine which failed to produce most of the symptoms associated with the actions of this drug. This indicates that salivary secretory activity measured in terms of this compound is a highly sensitive index of autonomic activity. Of interest also is the lack of a uniform correlation between changes in fluorophore concentration and flow volume. Changes in the latter with autonomic stimulation are usually attributed to increased blood flow through the glands. This would not seem to hold in the case of salivary fluorophore which is apparently independent of flow volume and thus may be secreted by the glands through a different, and as yet unknown mechanism.

The elaboration of a tyramine-like compound by the human salivary glands gives rise to a speculation which might be ventured at this point. This compound is closely related both as to chemical structure and biochemical origin to norepinephrine and epinephrine, both of which are neurohumoral agents. It is found to occur in saliva in amounts which, if constantly absorbed from the oral mucosa, may be significant, particularly with vagotonia; and by interaction with other amines might possibly participate in neurohumoral functions. If such speculation could be borne out experimentally, a hitherto unrecognized role might be ascribed to salivary gland function.

These and other aspects of human salivary secretion are being actively pursued in this laboratory.

SUMMARY

A tyramine-like compound has been detected as a component of human mixed saliva.

The secretion of this compound is apparently regulated by the autonomic nervous system, as seen by the changes in concentration following a single injection of autonomic drugs in human subjects.

Injection of urecholine gives rise to a definite response curve. Epinephrine also elicits changes in concentration, but not as uniformly as does urecholine.

There is no consistent correlation between changes in salivary flow volume and concentration of this salivary component.

The application of these preliminary findings to the study of autonomic function in man is discussed.

REFERENCES

1. Babkin, B. P. *Secretory Mechanism of the Digestive Glands*, pp. 748–751. Paul B. Hoeber, Inc., New York, 1950.
2. Cattell, M., Wolff, H. G. and Clark, Dean. The liberation of adrenergic and cholinergic substances in the submaxillary gland. Am. J. Physiol., **109**: 375–385, 1934.
3. Duggan, D. E., Bowman R. L., Brodie, Bernard B. and Udenfriend, S. A spectrophotofluorometric study of compounds of biological interest. Arch. Biochem. & Biophys., **68**: 1–14, 1957.
4. Furchgott, R. F. The pharmacology of vascular smooth muscle. Pharmacol. Rev., **7**: 183–265, 1955.
5. Goodman, L. and Gilman, A. *The Pharmacological Basis of Therapeutics*, p. 441. Macmillan Co., New York, 1955.
6. Hilton, S. M. and Lewis, G. P. Functional vasodilatation in the submandibular salivary gland. Brit. Med. Bull., **13**: 189–196, 1957.
7. Lourie, R. S. Rate of secretion of the parotid glands in normal children—A measurement of the function of the autonomic nervous system. Am. J. Dis. Child., **65**: 455–479, 1943.
8. Sprince, H. and Rowley, G. R. Quinine calibration of the Aminco-Bowman spectrophotofluorometer. Science, **125**: 25–26, 1957.
9. Strömblad, B. C. R. Amine oxidase activity in salivary glands. Acta physiol. scandinav., **36**: 137–153, 1956.
10. Strongin, E. I. and Hinsie, L. E. Parotid secretory rate in schizophrenic patients. J. Nerv. & Ment. Dis., **87**: 715–724, 1938.
11. Udenfriend, S., Weissbach, H. and Clark, C. T. The estimation of 5-hydroxytryptamine (Serotonin) in biological tissues. J. Biol. Chem., **215**: 337–344, 1955.
12. Waalkes, T. P. and Udenfriend, S. A fluorometric method for the estimation of tyrosine in plasma and tissues. J. Lab. & Clin. Med., **50**: 733–736, 1957.

PSYCHOLOGICAL STUDIES OF KORSAKOFF'S PSYCHOSIS: I. GENERAL INTELLECTUAL FUNCTIONS

MAURICE VICTOR, M.D.,[1] GEORGE A. TALLAND, PH.D. AND RAYMOND D. ADAMS, M.D.

INTRODUCTION

This paper presents the findings of some basic psychological tests which were administered to patients with the Wernicke-Korsakoff syndrome. Two standard tests, one for intelligence and one for memory, were used with a view to exploring the cognitive deficit characteristic of this disease. The following brief description of the clinical features of the Wernicke-Korsakoff syndrome is meant to provide an introduction not only to the present report, but also to several subsequent papers based on a more detailed psychological investigation of this disease.

Symptoms of disordered mental function are particularly prominent in the illnesses which result from the excessive use of alcohol. In general, they tend to cluster around two major psychic abnormalities and form two readily distinguishable alcoholic syndromes. One of these is a derangement of sense perception, *i.e.* illusions and hallucinations. These symptoms form part of a syndrome which includes tremulousness, convulsions, and in its most advanced form, autonomic and psychomotor overactivity. This syndrome, which is called delirium tremens, seems to depend not only upon prolonged inebriation, but ultimately on withdrawal from alcohol. For this reason it may be referred to as a withdrawal or abstinence syndrome. With rare exceptions, delirium tremens or the several components thereof, which may occur singly or in various combinations, is benign and transitory in nature.

The second major psychic abnormality is an impairment of retentive memory. It tends to occur in combination with opthalmoplegia, ataxia and polyneuropathy, and is called Korsakoff's psychosis or Wernicke's disease, depending on whether one stresses the psychiatric or the neurologic aspects of the illness. There are, to be sure, other disorders of the mind and behavior which occur in the alcoholic, and it is not intended to convey the over-simplified idea that all of them can be classified as one or another of these two syndromes. They are, however, less well defined and less well understood, and we hope to undertake their study at a later time.

The second of the two major mental syndromes, Korsakoff's psychosis, occurs in a relatively stereotyped clinical setting. Usually the patient is an inveterate alcoholic who has completely severed all social bonds, though the illness may occasionally develop in a non-alcoholic. In contrast to the abstinence syndrome, nutritional deficiency is of primary etiologic importance; alcoholic excess plays a secondary role, being responsible for the neglect of diet. The outset of the illness is marked by the acute development of ocular palsies and an ataxia of gait. The majority of patients also show mental symptoms which take a characteristic form. During the acute stages of the disease there is a fairly definite apathy and drowsiness, although at all times the patient can be roused. The attitude of the patient is one of disinterest and indifference. Spontaneous

[1] Neurology and Psychiatry Services, Massachusetts General Hospital and the Department of Neurology and Psychiatry, Harvard Medical School, Boston. This study was aided in part by a Research Grant, M-767 (C) from the National Institute of Mental Health, United States Public Health Service. The authors wish to thank Dr. Walter Barton, Superintendent of the Boston State Hospital for his cooperation in providing the subjects of Study 2; and Dr. Kenneth Herman, Miss Elisabeth White, Mrs. Alice-Marie Miller and Miss Marilyn Ekdhal for administering the tests.

speech and action are minimal; questions are answered in a perfunctory manner and there is no effort made to sustain a conversation. The patient appears to be unable to focus his attention on any one topic for more than a few moments. Frequently, he suspends the conversation in the middle of a sentence or he may simply turn away and close his eyes. The questions that are answered betray a disorientation in time and place; and, if one persists in questioning the patient, it is evident that impairment of retentive memory, especially for recent events, is one of the most prominent features of a general mental disorganization.

Under the influence of nutritional therapy, specifically of thiamine, there is a rapid improvement in the ophthalmoplegia and a somewhat slower and often incomplete regression of the nystagmus and ataxia. Simultaneously, the patient becomes more alert and attentive, more able to concentrate and to maintain a conversation, and somewhat less confused. After several days, the ocular signs become unobtrusive and if not looked for particularly may easily be overlooked. The initial clinical picture of profound confusion gradually gives way to a mental syndrome which is dominated by an amnesic dementia. This is characterized by a profound defect in retentive memory, a retrograde amnesia—and an inability to learn—all of this in a patient who may now be alert, cooperative and even able to participate in complicated psychological tests. This is the well-known Korsakoff's psychosis, the intellectual disorder of which is serious and more or less permanent.

With the further passage of time and continued maintenance of adequate nutritional status, further changes may occur. The majority of patients recover slowly but incompletely over many months to a year or longer. During this period they continue to show varying degrees of memory defect. Isolated past events are recalled but are reproduced vaguely with lack of proper chronology. This forgetfulness and inability to sort out events in their proper temporal relationship constitute the most characteristic clinical features of the recovery phase of Korsakoff's psychosis. If the patient is seen for the first time during this stage, and if memory function is not too obviously impaired, the connection of this syndrome with "classic" Korsakoff's psychosis may not be appreciated. In such patients, a diagnosis such as "alcoholic deteriorated state" or "organic brain syndrome due to alcohol" is usually entertained. A minority of patients, in contrast, change little or not at all even after several years and at all times are easily recognized as typical examples of Korsakoff's psychosis.

METHOD OF TESTING AND SELECTION OF PATIENTS

The main objective of our studies of Korsakoff's psychosis was to determine whether psychological tests would reveal any mental dysfunction other than amnesia and confabulation. The test procedures used, some well standardized and other specifically devised for this study, will be outlined in the several papers in which our findings are recorded. This paper only reports the results of tests with the Wechsler-Bellevue Intelligence Scale (5) and the Wechsler Memory Scale (6), which were chosen because they are widely accepted instruments and permit a quick general evaluation of intellectual functions in the adult. Our subjects, who numbered 38, were drawn from larger groups of patients, which had been examined and followed by two of the writers, and who were believed to show a fairly typical Korsakoff's psychosis. Histories obtained from friends and relatives in each case indicated that all the patients had been chronic alcoholics and that their diet had been grossly inadequate for months or years before the onset of the illness. At the time of testing the patients were no longer drinking. In the acute stages of the disease, all of them had the typical clinical picture of Wernicke's encephalopathy, including the

acute mental changes described above. At the outset, seven patients also had had delirium tremens. An alcoholic cirrhosis was present in six, but was well compensated and producing no mental disturbances. The data derived from the use of the Wechsler-Bellevue Intelligence Scale and Memory Scale were collected at different times, and may be conveniently presented in two parts, Study 1 and Study 2.

Study 1 was conducted over a period of two years, from July 1951 to July 1953, and included observations on 15 subjects. This group represented all but three of the patients admitted to the Massachusetts General Hospital with a diagnosis of Wernicke's disease over this two-year period. The three exceptions were excluded from this study because of serious medical complications (tuberculosis, decompensated cirrhosis). In general, the patients were drawn from the lower economic and social classes of Boston and vicinity. None of them had had more than a high school education, but all had completed grammar school. There were nine men and six women, who ranged in age from 29 to 51 years (mean = 45.5, SD = 8.2) at the time of this first admission to the hospital. All of these patients had been hospitalized during the acute stage of the illness.

The important fact, already mentioned, that the clinical course of the mental symptoms in Wernicke-Korsakoff syndrome is usually subject to considerable change, emerged from the observation of these patients on the hospital wards. An attempt was made to study the changing character of the Wernicke-Korsakoff syndrome by testing the patients at different stages in their illness, preferably when there was a clear indication of clinical improvement. Intervals between test and retest therefore varied according to the clinical progress of individual patients. The first test was usually administered shortly after admission to the hospital, the second after intervals ranging from three to 32 weeks, the third after further intervals of from nine to 28 weeks. Of the 15 patients originally tested, 11 were available for one retest and nine for two retests.

Study 2 was restricted to patients who had all reached the relatively stable and chronic phase of the disease. All of them were at the Boston State Hospital at the time of their testing and had been there for periods ranging from 12 months to over 12 years after the acute phase of the illness. The sample tested originally consisted of seven men and 15 women, of whom only one had been a subject in Study 1. When first tested on the Wechsler-Bellevue Intelligence Scale they represented an age group ranging from 31 to 74 years (mean = 53.8, SD = 9.6). Two years later 16 members of this group and an additional patient were retested with the W-B Intelligence Scale and were also given the Wechsler Memory Scale.

The group of patients in Study 2 represented about two-thirds of a larger sample of patients with Korsakoff's psychosis from which they were selected for being less damaged in their general cognitive functioning. All of them had a history of alcoholism and a social background similar to those of Study 1. In all of them, too, the illness had an abrupt onset, at which time ocular palsies, ataxia and general mental confusion were prominent. Neurologic examination at the time of psychological testing disclosed that the stigmata of Wernicke's encephalopathy, *i.e.*, a mild horizontal nystagmus on lateral gaze and/or a broad based, shuffling gait, were still present in 18 of the 22 patients.

RESULTS AND INTERPRETATIONS

The principal quantitative findings of the two studies are presented in Table 1 and in Figures 1 and 2. Group means of total scores and subtest scores are presented in Table 1 for the three tests of Study 1 and the two tests of Study 2, the figures in brackets being the mean scores of the restricted

TABLE 1

*Mean Scores on the Wechsler-Bellevue Intelligence Scale and Wechsler Memory Scale**

	No. of Pts.	Information	Comprehension	Digit Retention	Arithmetic	Similarities	Picture Arrangement	Picture Completion	Block Design	Object Assembly	Digit Symbol	Verbal I.Q.	Performance I.Q.	Full Scale I.Q.	Memory Quotient
Study 1:															
Test 1	15 (9)	7.9 (9.3)	7.5 (7.5)	8.3 (8.4)	6.2 (5.7)	7.0 (7.7)	6.3 (7.2)	8.7 (9.9)	5.3 (5.0)	5.2 (4.4)	4.2 (4.5)	93.5 (94.9)	89.1 (89.7)	90.8 (91.7)	74.8 (73.7)
Test 2	11 (9)	8.9 (9.0)	9.5 (10.1)	8.5 (8.1)	6.1 (6.0)	8.3 (8.8)	7.4 (7.3)	9.8 (10.3)	6.0 (6.1)	7.2 (7.7)	5.9 (5.9)	97.5 (98.3)	97.8 (99.3)	97.3 (98.4)	78.9 (78.4)
Test 3	9	10.2	10.3	8.4	7.8	9.2	7.7	10.5	6.1	7.0	7.2	102.5	100.7	101.5	88.1
Study 2:															
Test 1	22 (16)	8.2 (7.7)	8.6 (8.5)	7.3 (6.9)	6.9 (6.9)	7.8 (7.6)	6.1 (6.8)	8.7 (8.6)	6.4 (6.0)	9.4 (9.8)	4.5 (4.4)	97.3 (95.7)	101.0 (100.8)	98.5 (97.6)	
Test 2	17 (16)	9.2 (9.1)	9.4 (9.6)	8.6 (8.6)	6.0 (5.9)	9.6 (9.4)	6.9 (6.9)	9.0 (8.8)	6.2 (6.5)	8.9 (8.9)	4.2 (4.1)	101.4 (101.3)	102.2 (101.7)	101.0 (101.1)	78.7

* Figures in parentheses are means of restricted sample retested.

samples of nine and 16 patients who participated in each of the testing sessions. Figures 1 and 2 show the subtest profiles in the first and second studies respectively, based on the restricted samples available for repeated testing. For comparison the profiles of Wechsler's normal subjects in the corresponding age groups are also shown, *i.e.* the group 40–44 and 45–49 combined in Figure 1, and the age group 50–54 in Figure 2. Three findings are clearly apparent from the Table and Figures. First, performance tends to improve in the various tests on retesting; second, the performance level fluctuates more across the subtests in the Korsakoff group than in the normal popula-

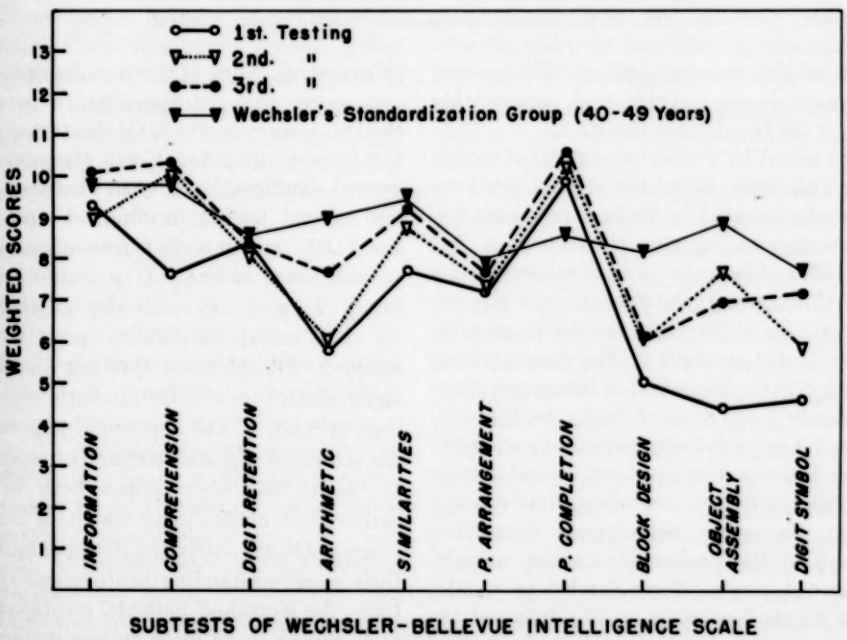


FIG. 1. Wechsler Subtest profiles, repeated testing, Study 1.

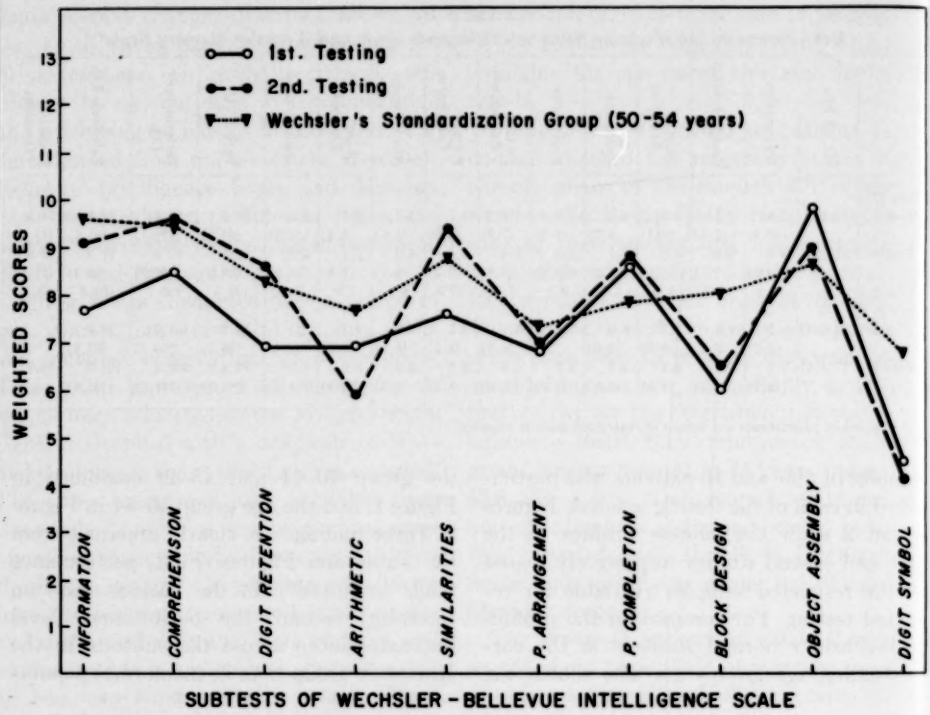


FIG. 2. Wechsler Subtest profiles, repeated testing, Study 2.

tion of the same age; third, the memory quotient is consistently and considerably below the Intelligence Quotient.

As tested by t ratio for correlated means, the Full Scale IQ of the nine patients repeatedly retested in Study 1 increased significantly ($p < .01$) between first and second, and again ($p < .05$) between second and third testing; the improvement was significant ($p < .01$) also for the 16 patients twice tested in Study 2. The same progress applied to the Verbal IQ in the second phase of Study 1 and Study 2, while the Performance IQ improved significantly ($p < .0001$) only between the first and second testing in Study 1, *i.e.*, following improvement from the gross neurological symptoms. Three of the performance tasks, namely, *Object Assembly*, *Digit Symbol* ($p < .01$), and *Block Design* ($p < .05$) followed the same trend during that period; the first of these showed further progress ($p < .05$) on third testing. None of the performance subtest scores changed significantly between the two tests in Study 2. Of the verbal subtest scores, that for *Comprehension* improved significantly ($p < .01$) between first and second testing in Study 1 and also ($p < .05$) in Study 2, *Information* in the second period of Study 1 ($p < .05$) and in Study 2 ($p < .01$), as did *Digit Span* ($p < .05$) and *Similarities* ($p < .01$) in Study 2. The Memory Quotient improved significantly ($p < .05$) on both repeated tests in Study 1. The improvement shown in the scores on repeated testing corresponded to the clinical observations both in the earlier phase of the disease and in the chronic stage. Although, after the disappearance of their more outstanding neurological symptoms, the Korsakoff patients' mental status may appear to be more or less stationary, many of them nevertheless continue to im-

prove at a slow rate, or at least to adapt more efficiently to the testing situation.

The profiles obtained by plotting the scores of all the subtests of the Wechsler-Bellevue Intelligence Scale at first appeared sufficiently consistent to suggest a pattern specific for the Wernicke-Korsakoff syndrome. This expectation, however, was not borne out by detailed analysis. In Study 1, ranking the weighted scores of the ten subtests for each subject, concordance as measured by Kendall's (3) W coefficient was significantly higher than chance at the .01 level (1) for the 15 subjects in the first test (W = .21, *chi sq.* = 30.1) and for the 11 subjects in the second test (W = 27, *chi sq.* = 33.0). In Study 2 the concordance was significantly higher than chance only in the second test with 17 subjects (W = .24, *chi sq.* = 38.4). However, concordances tested over repeated tests in either of the two studies or in both combined, were not higher than expected by chance at the .05 level. Correlations between mean rankings of the subtests were in the range of .65 to .89 but so were correlations between these and rankings based on Wechsler's control group. Thus, Korsakoff patients do not appear to have a specific profile on the Wechsler-Bellevue Intelligence Scale, even though they showed a fairly consistent tendency to score above their own mean level on such tasks as *Picture Completion, Object Assembly* (in the chronic phase) and to a lesser extent on *Comprehension, Information* and *Similarities.* On the other hand, they showed a relative failure with the *Digit Symbol* task and, to a lesser extent, with *Arithmetic* and *Block Design.* There was no marked tendency to score higher on verbal or performance tasks, except that on the first test in Study 2 the mean performance score was 4.7 above the mean verbal score (t = 2.6, $p < .05$).

In all of the Wechsler subtests, *General Information* was among the least damaged performances, confirming the clinical observation that acquired knowledge is relatively unaffected by Korsakoff's psychosis. The answers of many patients indicated that they had failed to keep abreast of events after the onset of their disease, *e.g.* by citing Hoover or Roosevelt as the present President. Their performance in the *Comprehension* subtest was also quite adequate, in keeping with their comparatively efficient and by no means irresponsible behavior in social situations. The fairly high score on the *Similarities* subtest would favor the idea that formal thought processes are relatively intact in Korsakoff's psychosis. The results of the *Digit Span* subtest were not quite so good, as might have been expected from earlier reports (7, 9). It should be stressed that low scores on this subtest were in many instances due to a wide discrepancy between the number of digits retained forward and backward, particularly in Study 2. This defect would thus be symptomatic of the Korsakoff patients' difficulty in shifting from familiar mental sets. *Arithmetic* was the subtest most consistently below the mean verbal level, and showed no improvement with time in either of the two studies. That poor concentration was probably responsible for much of the failure in this task is suggested by the finding that over half of the patients succeeded one time or another with a more difficult problem after failing with an easier one.

Of the performance tasks, *Picture Completion* and *Object Assembly* were the only ones which showed little or no deficit. Both these subtests demand the solution of simple and concrete problems and rely on long established knowledge. The former test was performed at a level high enough on first testing to allow for no significant improvement on repeated tests; the latter revealed quite serious disabilities at a time when the neurological symptoms had not quite cleared up, and then showed marked improvement through the later stages of the disease. The patients' performance on the *Picture Arrangement* test was representative of their general intellectual level. The fact that the scores on this subtest held up so well was unexpected, in view of the

serious defects shown by these patients in the sequential structuring of events, whether these be their personal experiences or related in the form of a story. The group means somewhat obscure the actual results, for while several of the patients managed quite well with the pictures spread out before them, others could not discern any connecting principle among the cards of a set, and treated them as so many discrete pictures which they proceeded to describe one by one. A few patients seemed to grasp the sequence of the story, for they could verbalize it, yet failed to arrange the cards accordingly. This and the *Block Design* task showed no improvement over time, the latter demonstrating the familiar defects of brain damaged patients, failure to differentiate figure from ground or to use surfaces divided diagonally between two colors. Successful performance on the *Digit Symbol* subtest involves several cognitive processes. The consistently low scores of the Korsakoff patients agrees with the expectation that not much learning would take place and, in addition, must also be attributed to a failure in shifting orientation from the models to the task; this, rather than loss of speed in visual-motor coordination, is consistent with other experimental results obtained from the same patients.

Wechsler's Memory Scale provided further evidence of the Korsakoff patients' severe derangement in the acquisition and retention of new information. The scores of this scale are so weighted that in the normal population they should be equivalent to the IQ within each age group. It is therefore of some significance that in the Korsakoff groups studied the mean differences between MQ and IQ were significant at the .0001 level of probability, as tested by *t* ratio, both in Study 2 and on the first and second tests of Study 1; the difference was significant at the .05 level on third testing. Clearly the cognitive processes tested by the Memory Scale were more severely damaged in the Wernicke-Korsakoff syndrome than other intellectual abilities. But even among the various subtests there was a variability of impairment, for the deficit was most severe in learning new associations, and remained so after other memory tests had shown different degrees of improvement.

When asked to recall *associations between word pairs*, patients in Study 1 frequently substituted other words, usually familiar associations, or combined two words which belong to different pairs. None of the patients failed entirely with the easy associations; on the other hand, nine of 15 patients were unable to learn any of the difficult associations on the first testing, and only three raised their scores significantly on future testing. Of the group examined in Study 2 only four could learn any of the difficult associations, and none scored higher than two.

The gradual clearing of the early confusional state showed up most strikingly on the questions relating to *orientation*. On first testing in Study 1, disorientation in time and space were universally present, and only three patients were able to state their ages correctly. In Study 2, every patient knew that the place of examination was the Boston State Hospital. Nine of 17 patients gave their ages correctly and five patients were even able to state the exact date.

In Study 1 the capacity to form *logical memories* from stories read to the patients was grossly impaired.[2] Occasionally the pa-

[2] Two stories were read to the patients:

Par. (*A*) Anna Thompson/ of South Boston/ employed as a scrub woman/ in an offiice building/ reported/ at the City Hall/ Station/ that she had been held up on State Street/ the night before/ and robbed/ of fifteen dollars/. She had four/ little children/ the rent/ was due/ and they had not eaten/ for two days/. The officers/ touched by the woman's story/ made up a purse/ for her.

Par. (*B*) The American/ liner/ New York/ struck a mine near Liverpool/ Monday/ evening/. In spite of a blinding snowstorm/ and darkness/ the sixty passengers, including 18/ women/, were all rescued/, though the boats/ were tossed about/ like corks/ in the heavy sea/. They were brought into port/ the next day/ by a British/ steamer/.

tient introduced new material, usually having some logical relation to the story, *e.g.*, mentioning a heavy fog, because of its common association with England, or suggesting that the ship had struck an iceberg. More commonly there were incorrect juxtapositions or combinations of isolated facts so that the meaning of the whole was distorted. This occurred in relation to one story or involved both stories. For example, the fact that an American liner struck a mine and that the passengers were brought into port by a British steamer were combined, the patient stating that the liner was hit by a steamer. Another combined the ideas of a shipwreck and the boats being "tossed about like corks in the heavy sea" by saying, "A cork came out of the bottom of the ship. That let the water in." In some cases there was a perseveration of isolated facts from the first story, and these were integrated into the second. Thus one patient said that the people on board the (rescue) ship took up a collection for the survivors (of the shipwreck). Another said that Anna had been tossed around on an island off the British coast, but was taken to port by the officers, whom she had told of her mishap at sea. Two patients reacted to the first story as though it were a true account; that is, they took it literally and concretely. One of these patients wondered why the children had not eaten for two days when their mother had money with her and the other commented that the woman had been slow in reporting her loss.

In Study 2 only four subjects introduced new words or ideas into their reproduction of the stories, *e.g.* giving a specific age to a character, or elaborating the circumstances. Apart from mistaken recall of names and numbers and the substitution of words such as torpedo for mine, or "rolled" for robbed, the errors were almost entirely those of omission. In this group there were two instances of perseveration from one story to the other, and one remarkable instance of condensation, when one subject reported that "several of the passengers were tossed over like corks."

Perservation of earlier designs in the *visual reproduction* task were common in Study 1, and occurred only in three instances in Study 2. Mental control as tested by counting backwards from 20 to 1, recitation of the alphabet, and serial additions by threes, showed the least impairment in both studies. Here also the test which required the most of the patient in terms of shifting from a familiar set proved to be the most difficult. Thus in Study 1 only one patient failed to recite the alphabet correctly and many others earned time credits; the same was true for counting backward from 20 to 1. However, ten patients failed one or more times on the test of serial addition, which requires a shift from the more practiced sequence of 3, 6, 9 etc. In Study 2 only two patients made an error in counting backward, there were also few mistakes in the alphabet; again, most of the failures occurred in serial addition, only four subjects performing this without a mistake.

COMMENT

In a general way the observations recorded in this study agree with previous reports of mental deterioration in Korsakoff's psychosis, *i.e.* they support the view that the central feature of this psychosis is an affection of retentive memory. In addition, our observations and the interpretations derived from them stress certain features of Korsakoff's psychosis that are not generally appreciated, the most important of which is the gradually changing character of the mental aberration. In the acute stage the mental disorganization may be so great as to prevent the patient from participating in any of the formal psychological tests. Later, though the cognitive impairment is still widespread, it is most prominent in tests of memory.

Another feature which deserves special emphasis is the widespread deterioration of cognitive functions, quite apart from

those which depend on memory. The test results disclosed that, most consistently, this failure was with the *Digit Symbol* Wechsler subtest and, to a less marked degree, with *Arithmetic* and *Block Design*. Applying the interpretations generally given to these subtests, the patients showed defects in learning ability in a new situation, in concentration, and in spatial organization and in verbal and visual abstraction. The relative degree of deterioration in different cognitive functions changes with the progress of the disease, more particularly as the symptoms of general confusion clear up. These features probably account for the fact that no stable profile of functioning could be determined for the disease. Nevertheless, it differs markedly in its characteristic intellectual defects from Hebb's (2) summary of test data in non-aphasic cases of deterioration.

Although it is true that memory suffers more than other cognitive functions, this statement deserves some qualification. In the first place, memory may not be unitary in function. The obvious impairment in Korsakoff's psychosis is the loss of recently acquired knowledge—an amnesia for events of the immediate past or of a period of weeks or months preceding the onset of the illness. In most instances there is also an impairment, varying in degree, of memory for events of the distant past. Two other abnormalities, ordinarily regarded as functions of memory, are equally characteristic of Korsakoff's psychosis. These are the inability to learn and to retain new information, *i.e.*, to form "new memories" and the derangement in the ordered time relations of long established memories.

One may suitably ask whether the mental defect in Korsakoff's psychosis can be reduced simply to a disturbance of one of these functions of memory or for that matter, to an abnormality in any one cognitive function. Some authors have attempted to do so. Wechsler (7) regarded the inability to form new associations as the core of psychological disturbance in Korsakoff's psychosis. On this basis, however, one cannot logically explain the impairment of memory for events which long preceded the onset of the illness. The inability to place experiences appropriately on a time scale has been considered by van der Horst (4) and by Williams and Rupp (8) among others, to be the fundamental defect. However, the observations derived from the Wechsler-Bellevue substests indicate that there is a considerable impairment of the capacity to think coherently and to reason with data immediately before the patient, *i.e.*, in circumstances where memory function is not the major factor. These findings strongly support the contention that the Korsakoff syndrome cannot be explained in terms of memory loss alone.

SUMMARY AND CONCLUSIONS

1. The Wechsler-Bellevue Intelligence Scale and the Wechsler Memory Scale were administered to two groups of patients with the Wernicke-Korsakoff syndrome secondary to alcoholism. The first study included observations of 15 patients, who were tested shortly after the onset of their illness and then at periodic intervals ranging from three weeks to 12 months. The second study was restricted to a group of 22 patients who had all reached the relatively stable and chronic phase of the disease and who were tested at periods ranging from 12 months to over 12 years after the acute phase of the illness.

2. The test results disclose a characteristic pattern of cognitive deterioration in the Wernicke-Korsakoff syndrome. There is, however, no evidence that this pattern is specific to this syndrome. The relative degree of deterioration in different cognitive functions changes with the progress of the disease, more particularly as the initial symptoms of general confusion clear up. Presumably because of this differential progress no stable profile of intellectual functioning could be determined for the disease.

3. Memory functions clearly suffer more severely than other cognitive processes, and the most marked and persistent defect is the low capacity for learning new associations or the retention of newly presented information such as short stories. This failure is particularly marked in tests or situations which require the reproduction of chronological sequences. The clinical disability of Wernicke-Korsakoff patients is largely accounted for by these defects.

4. The results of this study agree in general with previous reports of mental deterioration in Korsakoff's psychosis. However, attention is drawn to the defects in cognitive functions other than those directly dependent on retentive memory. The data also stress the gradually changing character of the mental abnormality, from the onset of the disease to the late stable stage.

5. Results obtained by the standard psychological tests used in these studies can only serve for a preliminary or tentative determination of the psychological profile of this disease. We have therefore regarded the conclusions presented here as a point of departure for a more intensive research geared specifically to an investigation of this cognitive damage in Korsakoff's psychosis. The results of this investigation as well as our observations on confabulation will be presented in future publications.

REFERENCES

1. Friedman, M. A comparison of alternative tests of significance from the problem of *m* rankings. Ann. Math. Statist., **11**: 86–92, 1940.
2. Hebb, D. O. The effect of early and late brain injury upon test scores, and the nature of normal adult intelligence. Proc. Amer. Philos. Soc., **85**: 275–292, 1942.
3. Kendall, M. G. Rank Correlation Methods. Griffin, London, 1948.
4. van der Horst, L. Über die Psychologie des Korsakowsyndrome. Montschr. f. Psychiat. u. Neurol., **83**: 65–84, 1932.
5. Wechsler, D. *The Measurement of Adult Intelligence*. 3rd ed. Williams & Wilkins Co., Baltimore, 1944.
6. Wechsler, D. A standardized memory scale for clinical use. J. Psychol., **19**: 87–95, 1945.
7. Wechsler, D. A study of retention in Korsakoff's psychosis. Psychiat. Bull. N. Y. State Hosp., **2**: 403–451, 1917.
8. Williams, H. W. and Rupp, C. Observations on confabulation. Am. J. Psychiat., **95**: 395–405, 1938.
9. Zangwill, O. L. Some qualitative observations on verbal memory in cases of cerebral lesion. Brit. J. Psychol., **37**: 8–19, 1946.

ABNORMAL MENTAL CONDITIONS IN INFANCY

KURT GOLDSTEIN, M.D.[1]

INTRODUCTION

Organismic behavior depends upon two factors: the structure of the concerned organism and the condition in which the organism is at the moment, and the "environment," the tasks which arise from it for the organism. All organismic behavior is directed by the tendency of the organism to realize its capacities as much as possible in the situation. This can be fulfilled in a "normal" way only if there is an adequacy between the capacities of the organism and environmental demands so that realization of its nature can take place. If such adequacy does not exist, then the organism comes into "catastrophe," shows disordered functioning which goes along subjectively with the feeling of anxiety (5).

Catastrophe occurs on the one hand when "inadequate" stimuli which normally are not effective gain in a particular situation such a stronghold that they are forced on the organism; on the other hand, when the organism is damaged in such a way that it is diminished in its capacities or their use.

The condition of infancy is in both respects suited to bring about catastrophes easily. In fortunate, "adequate" conditions of the outer world, the normal infant fulfills his functions in an orderly way: he changes between activities and rest; he performs what corresponds to his stage of development; sleeps much and when awaking he opens his eyes, often keeping them fixated to some "object" or "event" in the outer world and seems to feel comfortable; is, in a word, in a state of "well-being" (7). The expression on his face is one of quietness, showing a tendency to smile.

Certainly this quiet, happy state is not always persistent. We see even in the best-handled infant catastrophic reactions more or less frequently occurring. Because the human child is born in an immature state, it is often exposed to inadequate conditions in the environment, the more so the less the people around are aware of what is adequate to the particular state of development of the infant.

One of the typical catastrophic states is the experimentally produced "Moro response" (8), which occurs in sudden abnormally strong stimulation. The dependence of the entrance of catastrophe upon a discrepancy between stimulation and the capacity of the organism to cope with it shows here in the fact that in a more developed state of the infant (at the age of five or six months), it can no longer be elicited.

In respect to the relationship between maturation and catastrophe, one has to be aware that catastrophes do not only disturb the momentary behavior; they can hinder normal maturation and so the development of the capacities. Maturation—as much as it is an inner process—is set going by the use of the capacities which in turn presuppose a definite environment. With increasing age and correct care, demands and capacities will increasingly correspond. The effect of catastrophes and of the protective mechanisms (by which the entrance of catastrophes are more or less diminished) may create an impression of a mental abnormality in the infant.

The lack of adequacy of the human infant to react to outer world conditions has often been considered as an effect of an "atrophy of the animal instincts." Such a theoretical concept does not help us in any respect to understand the phenomena. I personally am inclined to doubt whether the assumption of instincts as determining factors of behavior is well founded even concerning the behavior of animals, still less concerning the human

[1] 1148 Fifth Avenue, New York, N. Y.

being (*cf.* 5, p. 183). I shall not attempt to interpret infant behavior on the theory of instincts because in my experience that hinders careful study of the facts. We are able to understand behavior from observable phenomena if we consider them in relation to the total condition of the infant and his environment.

These brief and general preliminary remarks will serve as an introduction to the analysis of some abnormal mental conditions observed in infants which recently came into the center of interest of psychopathology, particularly by the work of Kanner, Spitz, Mahler, Elkisch and others. This paper is a report of the continuation of previous research concerning the Moro response (3), the condition of the so-called idiot savant (1), and rigidity in feeble-minded children (12). I would like to refer further to a paper about the first smiling of the infant (7), in which the condition of the infant in the first year and the change of the infant's behavior through the development of the abstract attitude beginning at the end of the first year, is described in detail.

EARLY INFANTILE AUTISM: A RE-EVALUATION

The first abnormal condition in infancy I want here to consider concerns observations of Leo Kanner (9) which he has termed "early infantile autism" or "inborn autistic disturbances of affective contact." The description of the condition and Kanner's interpretation is generally known from child psychiatry textbooks. Kanner himself has again described it in the second edition of his text on child psychiatry (10). "The common denominator," he writes, "in all these patients is a disability to relate themselves in the ordinary way to people and situations from the beginning of life".... There is, "from the start extreme *autistic aloneness*, which, whenever possible, shuts out anything that comes to the child from the outside." From this "autism" all the other positive and negative phenomena which these children present are supposed to become understandable. A comparison of Kanner's findings with those which we have described in our "Case of 'Idiot Savant'" (12) brought us to the conviction that we are dealing in our patient with a condition similar to those Kanner has reported.

We also observed many of the phenomena Kanner has described. It seemed to me, however, that there are observable differences in the ways these children relate to objects, and to persons. We have taken a critical stand (12) concerning Kanner's interpretation of this condition. A renewed study of Kanner's cases has convinced me that the so-called autism and the "desire for the maintenance of sameness" could also be understood from our point of view, namely, that we are dealing with an impairment in the mental capacity, particularly of that function which we call abstract attitude. The observation of the idiot savant boy, described more than 10 years ago, studied over many years together with a number of other similar cases, has strengthened our original assumption of the underlying basic defect.

One difference seems to be that while our patients show extraordinary capacities in some performance fields, some of Kanner's patients obtained a very low Intelligence Quotient in the psychometric tests, and one-third remained mute. Even when language was present it did not serve to convey meaning to others. Some of Kanner's children presented the same extraordinary performances we have observed (9). They had a phenomenal rote memory for names and precise recollection of complex patterns and sequences, etc., which according to Kanner indicates good intelligence in the sense in which this term is commonly used.

Thus even in this respect there seems to be a certain similarity between the two groups. Why some of Kanner's children did not speak cannot be fully discussed here. The difference in language development may have been an influence on the general appearance of the children; more important,

it might have contributed to the impression of a severe lack of relationship of the children to persons, which was the primary symptom on which Kanner based his theory.

I should like in this discussion to concentrate particularly on the phenomenon of the different relationship of the children to persons and objects. Clinical observations leave no doubt that these children do relate or respond differently to objects, and to persons. In order to understand the cause of this behavioral difference, it seems to me appropriate first to consider the behavior of the normal infant.

In the beginning the normal infant does not discriminate behaviorally between objects and persons. Object or person does not exist for the infant. Both are experienced as no more than stimuli and reactions induced by them. What becomes a stimulus for the infant depends on whatever reaction mechanisms are mature in his particular developmental stage and on the "behavior" of the outer world which precipitates the "contact".

We assume that effective stimulation of the newborn organism represents a disturbance of equilibrium, and creates tension and disorder. The organism, separated from the mother's body, has lost the "adequate" condition of the womb, and is confronted with many catastrophes. It has to find a new "adequacy" if to survive and develop. That presupposes that the infant is protected against the dangers of the external world. This protection comes, except for the maturation of some inner mechanisms, from the activity of the persons around him. Thus we must consider both the capacities of the infant and the behavior of the persons in positions of influence to him, *i.e.* whether it is adequate or not to the capacity of the infant. But it is clear that these two sets of factors interact with respect to the abnormal infant's differential behavior toward objects and persons.

The first reaction of the normal infant represents what I have called turning-toward the stimulus (5), turning the stimulated sense organ toward the "object," *i.e.*, the place where the object from which the stimulus originates is located, accompanied more or less by an equivalent movement of the whole body. The so-called Moro response is a good example of such a reaction. One among many others is the closing of the hand of the newborn when the palm is stimulated. These reactions occur passively; the organism is forced to react if the stimulus is sufficiently strong enough.

This turning-toward the stimulus is not only the infant's first type of reaction but the most primitive reaction of any organism. Its effect is the elimination of the tension and of the disturbance of equilibrium which the stimulation produces. The organism then goes back to its "normal" condition. This reaction type is normally only a transient stage, being succeeded by more complex reactions as maturation proceeds.

Normally the turning-toward the stimulus represents only the first step of the performance, and is only artificially to be separated. It appears alone if an innate mechanism is not yet fully developed. For instance, the first not quite adequate attempt of the infant at sucking may be such a phenomenon. Turning-toward appears to be a characteristic further of all abnormal conditions, not only in immaturity of the organisms but in pathological conditions. It occurs, for instance, in brain injuries, and in "abnormal" conditions of the "environment": for instance, in sucking when the breastfeeding mother does not behave correctly. It always occurs if there is inadequacy between the organismic capacity and the demands on it.

As long as the infant is in a stage when he can only react with these "primitive," imperfect reaction types to stimuli, he is not in an adequate relationship to the world and needs the help which comes from "persons." This is so also during the development of the innate mechanisms in the first year, which alone do not guarantee the infant's ability to survive. The child's ability to be-

gin to free himself from permanent dependence on adults depends at least in part on his development of the abstract capacity, which increasingly enables him to organize himself and his world, and so to guarantee his existence.

The protection of people around him gives the infant the opportunity to become a human being. The organism is determined in its activities to realize its nature. This "self-realization" occurs in various kinds of relationships with the "world," which lets man live in various spheres according to the complexity of his mental organization.

I cannot give a description here of all the various attitudes by which man accomplishes this. I would like to discuss only those which are presuppositions for the development of the infant, and in reference to the explanation of the first smiling of the infant (7). During the first year of life the abstract attitude is not yet developed. Protection of the infant is an outcome of the use of this capacity by the persons around him. The world about him thus becomes so organized that the infant can gain an adequate relation to it, a relation corresponding to his particular stage of development. But this kind of relationship to the world is not sufficient; the infant cannot develop unless he acquires a specific relationship to persons, which represents a particularly important sphere of human existence, the sphere of immediate unity with the "other" (7, p. 182). To characterize this sphere it is important to note that the infant is already in the second period of his life, the first represented by the condition in the womb of the mother. In the first period he has lived with his mother in a somatic unity, totally dependent on the mother's condition. I feel it is justified to assume that he has already had some psychic experience, the experience of well-being which accompanies all conditions of "adequacy" and therefore also the adequacy of the infant in the womb. Birth essentially changes the situation of the infant. The unity between him and his mother is broken. But from the early appearance of smiling we can assume that a new adequacy is being established.

This new adequate relation between the infant and the outer world develops only through special behavior of the mother figure. This is the effect of an intimate bodily relationship between mother and infant, which develops as an expression of love on the part of the mother. Thus the intimate unity which was lost by birth is re-established. Thus the infant again experiences the feeling of well-being. The unity with the mother is a paradigm of the unity between human beings, which is part of man's essential experience and represents a normal sphere of man's mentality. It is the sphere in which man experiences all intimate relationships with others, in which he encounters and understands the other as a person like himself. This experience of unity is often neglected and its significance for human existence not sufficiently recognized in discussions of the structure of human personality.

It goes without saying that the individual development of this sphere is of particular importance for the establishment of a relationship to persons in general. This must be considered when one tries to understand the relationship of abnormal children to persons. But the development of this sphere is also of particular significance for the emergence of the innate reaction mechanisms which bring the infant into relation to the world of objects. These mechanisms are only imperfectly present in the first stage of life. Their full development is an effect of maturation, but maturation also depends on the "behavior" of the outer world, on the "adequate" organization of the outer world, and the behavior of the mother in both respects. This complexity of the development of the infant's behavior has to be considered in any evaluation of his relation to different parts of the outer world, objects or persons. This is especially pertinent in understanding the behavior of abnormal infants. It is, of course, very difficult to determine how much

of a relationship failure depends on inborn lack of mentality, or on lack of maturation due to a failure of external conditions, or on the behavior of the mother figure. Further, one must determine whether the behavior of the infant is really "normal" and fully developed, or only appears so. In this respect I would like to stress that making a distinction between a normal use of innate capacities, and a turning-toward reaction and its effects, is not always easy, for one may be deceived by an extraordinary use of the latter reaction. That, in my opinion, accounts for many mis-judgments about children with unusual endowment in special performance fields (12).

We have so far taken into consideration only the infant and the persons in positions of influence to him. But objects and persons do not present the same relationship opportunities for infants, particularly for infants with underdevelopment of the reaction types. Before discussing this point, it is necessary to say something about methods of determining mental defects of the children, particularly in the first year.

EARLY ABNORMAL BEHAVIOR

In our interpretation of the "idiot savant" we came to the conclusion that their symptoms could be interpreted as expressions of the impairment of the abstract attitude. Further consideration of the behavior of children observed by Kanner and of other similar children I have seen, revealed that this may not be sufficient for understanding the behavior of infants in the first year, that is, in the period when abstract attitude is normally not yet developed.

What is the cause of abnormal behavior during this early period? What produces the inadequacy? Very little is known about this. Such children are not often brought to a physician in the first year; they seem more or less normal to the parents, except, perhaps, for the fact that the infants are particularly irritable and inclined to have temper tantrums. Parents may be inclined to overlook behavioral deviations, particularly when they discover that the infants soon present performances which seem to reveal extraordinary gifts. As an example of the existence of abnormal behavior which is often not evaluated correctly, let us consider the description of the sucking of these infants. It may appear normal to the mother; the infant has no difficuties in this regard and develops well physically. But reports on the sucking procedure are lacking in explicit detail. Sucking, even for normal infants, is not always an easy task. It takes a little time until the baby becomes adjusted to the nipple; often he loses it, has difficulties in finding it again. This kind of behavior may be more noticeable in abnormal children. It would be important to learn whether the infant always has to be brought directly into contact with the nipple, whether he begins to suck when his mouth touches another part of the body of the mother, whether the baby sucks in a normal way, and the like.

Mothers of abnormal infants are often astonished and shocked to learn there is something wrong with the child, and eagerly stress that he was a normal baby, particularly in relation to nursing behavior. These mothers may not report or be concerned with certain observed behavioral deviations, because for them the behavior has nothing to do with nursing. But the movements in sucking and the intake of milk do not represent the totality of nursing behavior. There are preliminary activities before the baby gets the nipple in his mouth which belong to normal sucking behavior. The normal infant shows expressive movements of excitement before he tries to come into a definite position with respect to the mother's body. He touches the mother's breast, searches for the nipple when he does not immediately find it, sucks a certain time, stops, gets the nipple again, stops, finally is satiated and goes away from the nipple; the body, tense before, relaxes; often the baby falls asleep. One speaks of anticipatory postures and ac-

tions in respect to all these phenomena, although it is doubtful whether the term "anticipatory" is appropriate. Anticipation presupposes an abstract attitude which the baby has not yet developed. It may, then, be more correct to speak of *preparatory* movements which belong—as a first step—to the sucking mechanism, and we can assume from behavioral failures in this respect that the mechanism is not normally developed. One could consider that the sucking of these children represents an effect of the turning-toward reaction due to the touch of the nipple which the mother has presented, and that the continuation of nursing is the effect of a repetitive movement instigated by the stimulation of an intake mechanism set off by the milk. In any event, a proper evaluation of the sucking process will be contingent upon more careful studies of the nursing behavior of abnormal children. From what is known, I think we can assume that the sucking mechanism is not normal; that there is a lack of the adjustment mechanism of the baby to the outer world in general and to the mother in particular.

As much as we are inclined to consider these deficiencies as expressions of a defect in development, it is not improbable that the failure in these "anticipatory activities" may also be an outcome of the lack of relationship of the mother to the child. Kanner has mentioned such a lack of mother-child relationship. Parents of these children are often quite intelligent, but that may not increase, and may even hinder the ability to handle babies properly. Particularly when these parents discover the extraordinary performance development, sometimes as early as the end of the first year, they may become so interested in training the infants in this respect that they overlook the enormous significance of the slow development of what we have called the "sphere of unity" between infant and mother.

Concerning the lack of the development of the innate mechanisms, we appear to be dealing with the same developmental deficiency which later finds expression in the impairment of abstraction. More accurate observations of the development of these mechanisms are required for a decision as to causes of failure in adjustment to the world in the first year.

Lack of smiling, in others' and my opinion, is a significant example of the retardation of one such innate mechanism. Smiling is commonly considered as an expression of an early relationship between the infant and the mother, and its non-appearance could be interpreted as a failure in affect, in feeling toward "persons." My observations do not support this view, at least for early smiling. The fact that it is possible to evoke smiling in the infant by a very definite stimulus configuration, and that the smile disappears if the stimulus configuration is only slightly modified, suggests a "reflex-like" elicited inborn mechanism. That it is not exclusively an emotional reaction to a person is further demonstrated when one recalls that the infant also smiles in response to external objects. It could be shown that for the spontaneous or imitative appearance of the infant's smile, it is necessary only that there be an objective adequacy between the organism of the infant and the demands put on him.

My observations strongly suggest that the smiling movement is accompanied by a feeling of well-being, which occurs to some extent in all activities of "adequacy" (12, p. 178). Later on, when the child has developed the abstract attitude, smiling is connected with the experience of mutual relationship, and then shows characteristic differences which are understandable in terms of the child's relationship to persons. Lack of smiling in the early period indicates that there is something wrong in the development of the objective relationship of the organism to the "world" in general.

Thus with abnormal infants the innate mechanisms of the first year are not normally developed, and, their mental capacity in general is reduced to a primitive level

where the turning-toward reaction and some other innate reaction types are alone active. Although an enormous amount of research investigation will be necessary to clarify our understanding of the behavior of abnormal infants, we can certainly say that their behavior toward objects is not normal.

PRIMITIVE REACTION TYPES AND DIFFERENCES IN BEHAVIOR TO OBJECTS AND TO PERSONS

May not the fact that the infant has only primitive reaction types at his disposal account for the difference in his behavior to objects and to persons? Objects seem to present more reactive possibilities to the infant than do persons, even if he has only primitive reaction types at his disposal. The infant can grasp objects, move them, squeeze them, put them into his mouth; in a word, there is a varied performance repertoire available. We shall show later that the "complex" ways in which some older abnormal children handle objects can also be understood in terms of very simple and primitive activities. That they appear complex is the effect of the enormous endowment of these children in some particular field.

What the infant does with objects does not seem to us to be accurately described as the ability "to establish and maintain an excellent, purposeful, intelligent relation to objects" (9, p. 249). Is it really justifiable to assume that these children behave relatively normally toward objects, and abnormally toward persons, because objects "do not threaten to interfere with the aloneness" and persons do? Is it not more probable that, with only primitive reactions available, there is very little the infant can do with the person? Further, is it not possible that the lack of established emotional ties of the mother to the infant, makes it less likely that the child will come into contact with the mother?

The relation to objects, on the other hand, is not normal. Because of his primitive reaction level the infant does not come into a relationship with the *whole object*, as normal children do even in the first year. Abnormal children show only reactions to parts—to those parts they can do something with "adequately"—although it may seem as if they are reacting to the whole object. Similarly for normal infants; for them objects and persons are also indistinguishable in early life. Even what appears in the beginning as longing for the mother (crying when she leaves), is probably not much more than a "reaction" toward the mother as object. This reaction normally changes with the development of the sphere of unity, which unfortunately for these abnormal children does not develop normally.

The deficiencies of these reactions to objects show that they are not determined by specific differences of the objects. Abnormal children put various objects together in the simplest order, one alongside the other, or one above the other, or later in the way the objects could be used together in a special situation. The arrangement is determined seemingly by accident and then maintained. In another situation these children cannot use the same object in a different way. They arrange the same objects at another time in exactly the same way at the first, and objects which do not fit in this initial order or use are "neglected." More correctly, they do not seem to exist for the child. If, for instance, "blocks, beads, sticks have been put together in a certain way, they are always regrouped exactly the same way . . . After the lapse of several days, a multitude of blocks could be arranged in precisely the same unorganized pattern, with the same color of each block turned up, with each picture or letter on the upper surface of each block facing in the same direction as before" (9, p. 245). All this shows how little differentiated for the children the "objects" are.

Kanner notes that this kind of behavior takes place, even though there is no definite pattern or design. For what is happening here a design is unnecessary. The children cannot build or use a design: they are directed by primitive mechanisms. The world

organized in the sense of determination by the individual character of the objects has no meaning for these children. The only determination is the urge to do what they can do and what they have done before. To use another arrangement or order would require a change, and this is difficult, even for normal children, at this age.

Abnormal children, whose abstract attitude does not develop, maintain this behavior fixation even later and show a strong trend toward repetition. There is every reason to assume that the ease with which an activity is performed produces pleasure in these children (as it certainly does with normal youngsters). So they repeat with great pleasure, and repetition more and more becomes their main "play." Repeated activity has a great significance for their existence, and particularly so because their behavioral repetitions often bring them acceptance, encouragement and admiration.

The fixated and repetitive behavior becomes so dominant that even small and unobserved changes in their routine will hinder very well-developed performances. As an example, our patient who liked to play the piano could not perform when the instrument was in another room (12). Such changes can bring these children to despair. Kanner has mentioned a number of such observations (9).

It may be considered an expression of this primitive behavior when Kanner notes that, "the absence of a block . . . was noticed immediately and there was an imperative demand for the restoration of this missing piece. If someone removed a block, the child struggled to get it back, going into a panic tantrum until he regained [the block], and then promptly and with sudden calm after the storm returned to the design and replaced the block" (9, p. 245). I have repeatedly observed precisely this behavior not only in abnormal infants but in brain-injured adults.

Is it necessary for the explanation of these phenomena to assume an "obsessive desire for the maintenance of sameness" (9, p. 249)? I think not. I would also deny the existence of a special drive for repetition. It is sufficient to assume that the individual is urged to do something, and does what he is able to do in a particular situation, resisting demands that he do something he realizes he cannot do. When the demand is not so strong as to bring catastrophe, he seems not to "pay attention to it." Kanner makes this point only in relation to persons. "When the child was addressed, he was *not bothered* (italics added) . . . Comings and goings, even of the mother, did not seem to register. Conversation going on in the room elicited *no interest* (italics added) . . . If an adult forcibly intruded himself by taking a block away or stepping on an object that the child needed, the child struggled and became *angry with the hand or the foot* (italics added) . . . This corresponds to our assumption that he reacts in a similar way to 'persons' as to 'objects' " (9, p. 246–247). Is it necessary to explain this behavior by assuming that the person does not exist for the infant because he has no emotional tie to him? Is it not simpler and more understandable to assume, as I do, that with his primitive reaction types the child reacts only to "stimuli" and not to whole persons? The *stimulus was related to the hand or the foot* in this situation; therefore the child reacted to them. What for us appears as a part of a person, is for the child the stimulus he reacts to. Kanner says that, "it would be wrong to say that they [the children] are not aware of the presence of persons." I would agree in the general sense that they were aware of something, even of something they were acquainted with, but these children do not experience a person as an adult does. They were aware of what they could react to, the hand or foot, not the person. When the boy was pricked with a pin, "he showed fear of the pin, but not of the person who pricked him" (9, p. 247). I would even speculate that he was not afraid of the pin, but only of the pin prick. That parts of per-

sons can even evoke friendly gestures is indicated by Kanner's description of a child who walked between the observing adults, "gently touching a hand and a knee . . . as on another occasion he patted the desk." Persons are treated like desks, not because the child has no feeling for the former but—due to his primitive way of reacting—because he has only one way to treat both persons and objects.

I have suggested that it is superfluous to assume a special drive for the coming to the fore of this type of reaction. It is the expression of the *one* driving force which determines all organismic normal and pathological behavior, of the tendency of the organism to realize its potentialities as well as possible. If under abnormal conditions the individual is deprived of normal performances and yet is urged to do something, he has no alternative but to do what he can still do, to exercise those forms of reactions which are preserved. In the early life of an abnormal infant the "turning-toward reaction" is the extent of his repertoire; it is the only reaction form which permits him to come into an adequate relationship with the "world" and so actualize himself in striving to cope with the world. He sticks to it under all circumstances, and he comes into catastrophe when something is demanded of him that cannot be fulfilled in this way.

If we return to the exploration of Kanner's concept that these children have "an inability to relate themselves in the ordinary way to people and situations from the beginning of life," we would agree with his interpretation, presented in this general form. What we call a mental defect which concerns the innate reaction forms—normally maturing in the first year, and the abstract attitude which develops later—certainly produces such a disability. But we cannot agree with Kanner when he sees as the basis of this deficiency "inborn autistic disturbances of affective contact" and "a powerful desire for aloneness and sameness" (9, p. 249, 250).

No doubt these children have a lack of affective contact and are living "alone"; no doubt that they have a need for "sameness" of performance. But we see in these anomalies an expression of the underlying mental defect. Our analysis of the latter and the characterization of the capacities preserved enables us to understand in all details the failures these children present as well as their fixated performances. The influence of such primitive mentality on behavior toward persons and objects made it appear that these children were in better relation to objects than to persons. Qualitatively, however, their behavior was the same in respect to both realms of the outer world. It corresponded to the primitive approach which brings them, in principle, into the same kind of contact with objects as with persons.

CONTACT WITH PERSONS

There is still another factor which makes it more difficult for these children to come into contact with persons—the deficient development of the "sphere of unity"; the sphere which is of particular significance for the baby's well-being and so his development in general, but especially for coming into relation to persons. For the development of this sphere of unity adequate behavior of the mother is of paramount importance.

Kanner's observations, like my own, show that the parents, and particularly the mothers of these children, were often not well suited to handle the baby in an adequate way. Parents of these children are often especially gifted persons, intellectual and ambitious, and their own high intelligence makes them overly interested in the development of the "intellectual" capacities of the infant. This is most often true when the child's extraordinary gifts come to early observation, and it is to be expected that the immediate relationship between mother and infant is somewhat neglected.

In such instances the bodily relations be-

tween mother and infant, which develop specifically from the expressions of love on the part of the mother, are not as much in the foreground as normally. And as a corollary the development of feeling and expressive movements on the part of the infant is more or less retarded.

Thus we would conclude that the difference in the relation of these children toward persons and objects is a result of the lack of inborn mental capacity and the behavior of the environment, particularly that represented by the mother toward the infant.

It is interesting that interactive contact with persons increases when these children grow up. When, some years later, these children are observed with other persons who behave toward them in an adequate way, they show much more contact than one would expect on the basis of their behavior during the first year. For the development of the personal relation, the abstract capacity plays an essential role. The lack of abstraction, however, cannot be made responsible for relationship failure in the first year, when no infant has this capacity.

Because the physician sees the child only occasionally and not in his everyday life, this later development of relations to persons may be overlooked or incorrectly evaluated. Thus it is important to try to obtain more accurate information about the relationship of the child to other people. The mother may well be neither the best observer nor informant. We can, perhaps, rely more on a teacher who is with the child several days in the week or daily for some hours, particularly if the teacher has been well informed about the child. She is in a position to be able to report a wide variety of interpersonal situations and episodes that may be enormously revealing. I have found it very helpful to observe and examine the infant in the teacher's presence.

From my experience I would say that older children, from six to eight years of age, come into contact well and try to come into contact with persons. But they establish contact only with those with whom they have something in common, and with whom they can do something they are interested in doing. Their contacts rise out of common activities or definite activities in relation to other persons.

In a variety of play situations and activities with the teacher, these children can be brought into close physical relation to the teacher. They may embrace her, use the words which they have heard her use, perform activities which they are asked to do and like to do. This kind of behavior can occur only in definite ("adequate") situations into which the children come passively, as a result of skillful arrangement and manipulation of the environment.

The mental defect these children suffer from, and in particular their impairment of abstraction, requires this kind of planned environment for them to acquire their sometimes considerable knowledge and performance ability. My recent experience and the detailed study of Kanner's reports have confirmed our previous observation that these children cannot learn by any direct teaching methods. In view of their ofttimes enormous knowledge and increasingly new acquisitions this may appear paradoxical, but it is understandable if one recalls that they must learn in an indirect way, by somewhat passive repetitions of what they experience in adequate situations. This repetition takes place compulsively, but it would be incorrect to say it is the effect of a drive for repitition. Rather, it is an effect of the tendency to do what they can do, accompanied by feelings of pleasure, of the pleasure normal children also feel in doing something easy to do which has some positive effect. Pleasure is increased by the praise and appreciation they get from their environment. In this connection I would note Kanner's remark that one of his children four and one-half years old, "took great pains in attracting the attention" of the examiner who had praised him (9, p. 238). This would not be possible if there were no relationship. In

this instance the physician was apparently able to bring the child into the sphere of immediate relationship.

It is understandable that this kind of contact may develop only with special persons. But when the child is confronted with an "adequate situation" involving several persons of whom he knows only one or two, I have observed the following. After the child speaks to or otherwise relates to the known persons, he will attempt to establish contact in the same way with others unfamiliar to him.

The contact always develops out of a situation which the child can handle, according to his particular endowment or capacity in one or another field. In those children, for example, who have developed an arithmetic capacity and knowledge concerning the calendar, this skill becomes a very good means of coming into social contact. In children particularly gifted in the field of music, contact will easily develop with a musician, and so on. One has the impression that in these situations a feeling relation, an emotional tie, may develop between the child and the person exemplifying the common sphere of interest.

PSEUDO-SOCIAL BEHAVIOR

Experiences with brain-injured patients with impairment of abstraction have made me very cautious in the evaluation of such "personal relationships." Such patients can behave "normally" in social situations with others, as, for instance, in a particular group situation, or at dinner. But closer investigation shows they are not connected in the usual way by emotional ties with the members of the social group. I have referred to this as pseudo-social behavior. I would like to refer to a previous discussion of this phenomenon and describe as an example the behavior of one of these patients in relation to his family.

The patient, a married man, had been in the hospital a long time and "never spoke" about his family. He was unresponsive when questioned about it, and when the suggestion was made that he write or visit them, he showed indifference. He seemed to lack all feeling. It was an established practice for patients to visit their families from time to time. While at home he conducted himself quite normally (as we learned from the members of his family), was kind and affectionate to his wife and children, interested in their affairs as far as his general mental ability would permit. After his return to the hospital, when asked about his family, the patient would smile in an embarrassed way, giving evasive answers. He seemed utterly estranged from his home situation. From this and many similar observations of patients with impairment of abstract attitude, we came to the conclusion that when the patient does not react emotionally in a satisfactory way, it is in situations in which he also fails to comprehend the essentials to which a definite feeling attaches. Equally with these children: they react to persons emotionally if they are with them in an adequate situation, where in general they react normally. They appear, indeed, to be more disturbed in these relations than the adult brain-injured patients, because the children cannot react to previously acquired "social behavior."

The ties to persons are very easily broken in abnormal children, as well as in the brain-injured. Seemingly unimportant and easily neglected behavioral deviations change the feelings, destroy the personal relationship and bring the individual into catastrophe.

The abnormal child comes into better social contact by reason of his gradual acquisition of performance skills. At the same time these improved relations to persons tend to further increase his knowledge and his activities. If one observes these children only in the first years, one is astonished at seeing how they can later develop a number of such seemingly complex activities. This cannot be the effect of a development of abstract attitude; psychometric examination shows no change in abstract conceptualiza-

tion. Thus it is of interest to try to determine how such children acquire these skills. As an example, a twelve year old boy was able to help his mother in relatively complex household activities. Among other things he could help with work in the kitchen, cleaning and putting things away properly. He could cook, using the proper ingredients. He could shop at the grocers', obtaining the desired items without error, and paying for them accurately. To get a direct insight into how this youngster had acquired these concrete activities, would, of course, have been scarcely possible. One could not arrange experimentally to investigate them, and any direct request to perform a given activity had the effect of blocking, produced active resistance and temper tantrums.

With the help of competent observers it is possible to register some details about the ways in which children acquire these activities. There follow some examples as illustrations.

Use of the telephone. One day after the boy mentioned above had seen his mother using the telephone, he picked up the receiver and spoke into it. He had, of course, seen his mother dial before speaking, and he tried that. After he had discovered that definite persons and numbers belong together and are listed in the telephone book, he turned to the directory, looked up the number of his teacher and dialed it. To bring together the series of numbers in relation to the motor movements of dialing was not difficult for him. He then held the receiver to his ear, as though waiting for something to happen. After a time he recognized the ringing tone and seemed to know that after this tone he would hear a voice. He might wait for a long time. If the call was not completed—if, for example, he did not eventually hear the voice of his teacher —he might say "Mira (his teacher) is on vacation." If the teacher answered the phone, he would respond to her questions in his habitual primitive way. Throughout all this he would not initiate any part of the conversation, but simply respond to questions. If the teacher stopped talking, he would not ask whether she was still there, but merely continued to listen.

The whole procedure is entirely understandable. It is instigated by a concrete situation, the presence of the telephone and a desire to be together or communicate with the teacher. This may have come passively into his consciousness and produced the activity of telephoning with its concomitant behavior. Although he may say, "Mira," he cannot otherwise speak unless he hears her. Seemingly the teacher's image is necessary for him to begin speaking, and he cannot create her image. All his activities are responses to stimuli: there may come into his mind a recollection that causes him to say "Mira is on vacation," or he may scream. In this situation he can react only to the auditory stimulation, and not to a person he does not see or hear. He may stay at the telephone for as long as he is not stimulated to do something else.

Bicycling. This same youngster had seen boys bicycling and wanted to learn to ride. He met with no success on the basis of definite instructions as to pedal manipulation, steering, and balance. But when he was physically assisted to mount, to move his feet on the pedals and to steer, he was able to make some progress. He continued to practice the activity in this way, by himself, and was soon able to keep his balance and ride without accident.

Buying in a store. This boy was able to shop successfully for his mother only if there was *concrete and situational determination.* When he realized that his mother needed something, he was eager to go to the store. He would repeat, in quantity and kind, exactly what his mother wanted him to buy. He would ask the grocer for the needed items, compute the cost, and accurately and quickly select coins for payment. He was reported never to make a mistake.

From these and other examples, one sees that these children "learn" only by doing;

through specific movement and activities they can be brought into contact with a desired task. Such a child must want to perform the activity in question; he does nothing on the basis of instruction or demand. He does not learn through demand; all of his activities must rise out of a particular concrete situation and his past experiences in relation to it.

SYMBIOTIC PSYCHOSES: A RE-EVALUATION

The discussion of the condition of the children called "idiots savants" and of the autistic children described by Kanner, leads inevitably to a consideration of the symptomatology of children with "autistic and symbiotic psychoses," as reported by Margaret Mahler (11). Mahler sees underlying the autistic psychoses a condition similar to Kanner's early infantile autism. "In autistic infantile psychoses there are no signs of affective awareness of other human beings" (11, p. 290). It is difficult to determine whether Kanner's and Mahler's use of the term *autism* is precisely the same. From their explanation of the origin of the condition, one might think that attention is being focused on different causes and disturbances occurring in different stages of development of the infant. While Kanner assumes that the abnormal condition is related to an inborn defect of affect, Mahler bases it on the conflicting situation in the most important transitory stage in the adaptation to reality, "that step in the development of the sense of reality in which the mother is gradually left outside of the omnipotent orbit of the self." Thus Mahler points to the causal difficulties as originating in a definite stage of development.

This position is not inconsistent with our own, if attention is paid to the second period of life, that period characterized by the development of the abstract attitude. Yet we see the defect differently in the children described by these two investigators. We can agree with Mahler's position when she stresses that, "it is very difficult to ascertain whether the grave disturbance in a case of early infantile psychosis has been caused by the mother's pathology or lack of sympathy or by the infant's great innate ego deviation, be it an inherent lack of contact with the living environment or an inordinate need for symbiotic parasitic fusion with the adult" (11, p. 288–289). We would, however, characterize the two factors somewhat differently. We entirely agree with Mahler that the development of the abnormal condition depends on an inborn factor *and* the behavior of the environment, particularly the mother. But the "inherent lack of contact with the living environment" would seem to me to be the effect of an inborn defect—a defect of the development of those innate adjustment reaction types characteristic of human beings.

The organism's development and maturation is not an independent phenomenon, but depends on the condition of the environment, and especially on the behavior of the mother. This, then, can modify or disturb the maturational development of the infant. The behavior of the mother is important not only for the development of the adjustmental reactions of the infant, but also for the reestablishment of the so-called close physico-psychic unity between child and mother, that has been disturbed by the event of birth. This is particularly important for the further development of the infant's relationship to the world, especially to persons, and these relationships are virtually always disturbed in the "child psychoses." A clear understanding of the origin and organization of the physico-psychic unity is necessary for an appreciation of Mahler's assumption of a "symbiotic-parasitic condition and the inordinate need for this symbiotic-parasitic fusion as the *one* cause of the ego deviation of the infant.

From my point of view, we have to see in normal development a belonging-together of mother and child, originating from adequate behavior of the infant *and* the mother. I am very doubtful that the baby has the

feeling of a parasitic condition in relation to the mother's body.

If the infant is in a condition where he can realize his possibilities as related to his stage of maturation, he then experiences "well-being" in "adequate" events; otherwise he experiences anxiety in inadequate conditions. The infant experiences neither dependence on the mother, nor a feeling of oneness with the mother's body. In my view he is not a parasite with respect to the mother, nor does the mother commonly experience him as such.

What may *appear* as symbiotic parasitism is clearly different from normal behavior. On the one side it consists of the feeling due to abnormal "stimulus boundness" (5, p. 154) of the infant, the consequence of the defect of adjustment reaction types; on the other side, it may be an expression of the abnormal feelings of the mother due to her character and her own reactions to this abnormal behavior of the infant. In turn the mother's reactions have their effect on the development of the baby, on his "sticking to the mother," and may have an after-effect on his later behavior. Let me stress here that there is no reason to assume an inordinate need for "symbiotic parasitic fusion," as if the normal child would be driven by a lesser need of this kind. This fusion is the effect of a *pathological reduction* of normal adjustmental behavior to the primitive (abnormal) turning-toward behavior. The "deviation of the ego," I would further submit, is not the effect of this pathological behavior. It surely contributes to an impairment of maturation, but it is more than doubtful whether this alone can hinder ego development. An impaired ego development is the effect of an inborn mental defect as revealed in the deficiency of the abstract attitude.

Mahler writes that, "There are infants with an *inherently defective* (italics added) tension-regulating apparatus which probably cannot be adequately complemented by either the most quantitatively or qualitatively efficient mothering. It seems that there *are* infants with an *inherent ego deficiency* (italics added) which from the very beginning—that is to say, from the stage of the undifferentiated phase—predisposes them to remain or become alienated from reality; there are others whose precarious adherence depends on delusional symbiotic fusion with the mother image" (11, p. 289).

I would hesitate to speak of such an inherent defective tension-regulating apparatus but would rather think of an inborn defect of reaction mechanisms and a reduction to the more primitive ones, *e.g.*, the turning-toward reaction. An abnormal clinging by the infant to the mother ("symbiotic fusion with the mother image") may be brought about by an inappropriate reaction by the mother to the primitive behavior of the child. I think both Kanner's and Mahler's terms are somewhat ambiguous. The abnormal behavior, in my opinion, can be interpreted simply as secondary to a basic defect. I do not know whether we are justified in speaking of autistic behavior in so early a period of life. We are here dealing with a persistence of primitive behavior, probably essentially different from the autism seen in more mature individuals. In foregoing the assumption of a "symbiotic fusion with the mother image," we would not have to assume the "precarious adherence" required by this concept. The infant is not forced to be symbiotic by a delusion, but (by reason of his defect and the mother's behavior) because he simply cannot react differently.

We would not be satisfied to consider the abnormal behavior of these children as simply an effect of the lack of development of abstraction, and in this sense we are certainly concerned with the influence of environmental factors. The outbreak of the "psychotic state" is an expression of the fact that demands are made which the child cannot cope with, and intensity of the disturbance will be determined by the strength of such demands. Thus it is important to note Mahler's comment that the mother frequently displays a prominent psychopa-

thology. This is considered to be an "extrinsic factor in the genesis of the symbiotic psychosis" (11, p. 293).

Significantly, some of Mahler's reported observations suggest that these children have a characteristic mental defect similar to that of the "idiot savant." This would tend to support our assumption that we are dealing with an inborn mental defect.

Mahler reports one case, in part, as follows. "At the age of three and a half Lotta had no language, no gestural communication, no hand, mouth and eye integration. She neither fed nor handled herself and she showed a terrified startle reaction at any touch *of* or *by* another person. [How she behaved to any sensory stimulation by objects we do not learn.] By the usual intelligence rating she would have ranked among the lower imbeciles. However, Lotta's habits were compulsively neat, her motor and manipulative skills were age-adequate, her knowledge of, her memory for, her static inanimate environment were phenomenal" (11, p. 290).

This difference between measured intelligence level (I.Q.) and the ability to perform adequately in real-life situations, was found to be characteristic of idiot-savant children. One is immediately reminded of this by Mahler's further remark that Lotta, in therapy, "was slowly brought to sensory perception of the outer world by gradually accepting contact with the analyst's body." We have made similar observations in studying such children, and should add that it is important for the therapist to behave in such a way as to make it possible for the child to come into close physical relationship.

But we found that this kind of relationship did not constitute a better adjustment to the world or to all people. I have had the impression that the close physical relation (which had the character of a "symbiotic clinging"), was more the effect of a better insight by the therapist or teacher into the needs of the child, *i.e.*, of an adjustment of the physician or the teacher to the condition of the child, than of a better relationship on the part of the child himself. This was evident when a child who "related" well to a certain person in a particular situation, became very reluctant or withdrawn from the same person under different conditions. To my mind this is simply an effect of the primitive reaction type which all these children possess. It would seem to be the case with Lotta—particularly in the context of Mahler's remark that no normal identification occurred. The child's difficulty in making even this kind of "pseudo contact" must be the effect of a mental deficiency, not of an autism. Other symptoms which Mahler mentions point in the same direction as for instance, that, "no normal identification occurred but instead there was extensive mirroring and parrot-like word formation. Word formation was autistic and speech was not used for intercommunication but only for commands and signals . . . "

Mahler does not report results of extended special examinations, but some few of her observations allow the conclusion that symptoms are due to a defect in abstraction, as in our children. When Mahler writes that, "speech was used toward objects as freely as toward the analyst," this suggests that the analyst was experienced as not different from objects in the environment. I am reluctant to accept the observation that the child "seemed to catch up rapidly with isolated fragments of her arrested ego-development."

I am equally reluctant to accept Mahler's interpretation of the further description of this child's behavior, when it is reported that, "She went through repetitious, aggressive exploration of her inanimate environment—banging the doors, switching the lights on and off and fingering everything like blind people do." From my point of view this child had no ego and was not exploring objects as normal children do. She was not aggressive in the accepted sense of this term; she was simply affected by stim-

uli and reacted to them primitively, adequately where possible, otherwise not at all or with catastrophic reactions. She experienced only "parts" of the outer world, and of her own body. But these are not parts of a whole object as perceived by normal children; rather, an object-part was the only stimulus she could react to adequately. That an emotional relation was lacking, even when she seemed to be in "symbiotic relation to persons" is in my opinion not an expression of missing affects. Whether one should characterize the driving forces as libido and aggression, which only "exist in an unneutralized form due to the absence of the synthetic function of the ego," or whether it may not be that these children simply react to what they can handle adequately with their primitive mental capacity, I leave to the reader to decide.

I am, in summary, inclined to assume that children with autistic psychoses are one with the group we have described as "idiot savant."

We have found that "idiot savant" children, particularly in their repetitive activities, sometimes appear to be autistic, *i.e.*, out of contact with persons. On other occasions they seemed "in contact." Thus there is a certain similarity to Mahler's observations, particularly when she writes that, "the two types of infantile psychosis . . . can in many cases be clearly differentiated in the beginning. Later the pictures tend to overlap. . . . When we meet cases of child psychosis at a later stage, it seems that pure cases of autistic child psychosis as well as pure cases of symbiotic-parasitic psychosis are rather rare, whereas mixed cases are frequent; by this time symbiotic mechanisms have been superimposed on basic autistic admixtures and vice versa" (11, p. 301). This difference between early and later symptomatology needs explanation. It would be important to consider the complexity of developmental conditions, changing behavior during each stage, and the complex influences of inborn defects and environmental factors. A fuller understanding may make it unnecessary, even impossible, to distinguish two types of "infantile psychosis."

SYMPTOMATOLOGY OF THE SYMBIOTIC PSYCHOSIS

Behavioral descriptions of these children in the first year vary widely. On the one hand, they are described by mothers as "cry-babies or oversensitive infants"; on the other hand, the children "rarely show conspicuously disturbed behavior in the first year of life." But may not their clinging to the mother in itself represent an abnormal condition? If, as we assume, these children are indeed mentally retarded or defective, their activities may have been reduced to the turning-toward reactions. This condition might well combine with the abnormal behavior of a mother who considers the child an "appendage to her body," to produce an abnormal "symbiotic" state. The lack of adequate adjustmental behavior of the child will increase his clinging to the mother's body. And the deficiency of the normal mother-child unity is compensated by the abnormal "symbiosis," resulting in an adjustment that appears to be normal.

The disturbance comes to the fore later, at the time when the normal child begins to grow out of his dependency on the mother. Abnormal children develop frank symptoms, notably panic reactions, particularly in the third or fourth year. Typically they become upset when they are separated from the mother by placement in the nursery, entrance into school, birth of a sibling, and the like.

Anxiety reactions are so intense and so diffuse that they are "reminiscent of the organismic distress of early infancy." I would refer to these as catastrophic reactions. In the first years the normal child is able to tolerate some separation from the mother without coming immediately into distress, anxiety and "psychosis." The abnormal child cannot develop such independ-

ence. Mahler suggests that such a child has an abnormal tendency to "restore the narcissistic fusion, the delusion of oneness with the mother and/or father."

Therefore, one may get the impression that the symbiotic symptomatology does not appear in early life. Symptoms in "autistic" children appear earlier because they are the effect of the inborn mental deficiency and a particular kind of inadequate reaction of the mother, who does not provide behavioral opportunities for contact with the child. There are many similarities in the ways so-called symbiotic and autistic children react to the world. They are very excitable, restless, cannot concentrate, and are perseverative. The "symbiotic" children, kept from overt abnormal behavior by the opportunity of clinging to the mother, do not even appear "conspicuously disturbed."

If we assume that the "symbiotic" condition already exists in the first year, the later symbiotic behavior is seen as an aftereffect of previous abnormal behavior—increased by new demands which belong to the later period. These new conditions bring the child not only into increased symbiotic behavior, but, when separated from the mother, into catastrophe or psychosis-like conditions. This can be understood without having to assume that "the illusion of the symbiotic omnipotence is threatened."

These difficulties will increasingly occur at the time when dependence on the mother is usually lessened. They will, of course, occur the more when the mother herself is a psychopathic individual. Mahler considers such a condition of the mother "the extrinsic factor in the genesis of the symbiotic psychosis" (11, p. 293).... "The adult partner very often seems to be able to accept the child only as long as it belongs as a quasi-vegetative being, an appendage to her or his body."

This kind of situation will worsen if the psychopathic mother does not encourage the child's dependency. Mahler speaks of a mother who became so "harassed" as to place her child in a boarding school. Under such frustrating situations even such symptoms as hallucinations may develop. Children of this age, particularly those with a defect of abstraction, do not yet distinguish between images and real objects. The image of things to which they are particularly attracted and which they can handle in real life, may become so vivid that they react to them as to real objects, often becoming very upset if hindered from doing so (4). On the other hand, the child may not react at all to the outer world, may be mute and motionless, giving the impression of "catatonia." Behavior of this kind may suggest psychosis, and may further suggest that these children are not always "symbiotic"; sometimes they may even appear the opposite, withdrawn and autistic. This occurs especially when "the ego of the symbiotic type is overrated and expected to be able to cope with reality without continual ego fusion from the therapist." Then "withdrawal into stuporously autistic states or hebephrenic deterioration," may occur (11, p. 303). Children of this kind react in ways closely reminiscent of brain-injured adults with impairment of abstraction. In the latter instance the stupor-like behavior is considered to be an expression of distress and frustration, stemming from discrepancies between demands and impaired capacities. The reactions of brain-injured patients represent expressions of protective mechanisms, occurring passively as a means of safeguarding the patients' "existence" in situations of unbearable distress and anxiety. The more such a patient is deprived of the abstract ability, or the more it is needed for a particular task, the more abnormal behavior is observed.

SUMMARY AND CONCLUSIONS

It is unnecessary, then, to consider the autistic and symbiotic psychoses as two different diseases. Rather, they can be thought of as different symptom complexes, due to different reactions determined by the same

underlying anomaly or defect in development. These reactions take place under different conditions, different environmental demands and varying degrees of protection against catastrophe by the people in positions of influence to the child.

The "autistic" reaction type is most apparent in the first year if environmental circumstances do not allow a close relationship to develop. The behavior of an "autistic" child does not totally prevent his coming in contact with the world of objects and persons, but the extent of the contact depends on the behavior of the people around him.

The "symbiotic" reaction type is not, like the autistic, the effect of a kind of neglect of the mentally abnormal child, but rather the effect of an inadequate influence on the child during early life.

There is certainly no doubt that for normal development and normal contact with persons and objects, human love is a prerequisite, but whether an emotional attachment develops does not depend only on the mother. Also critical to this is the normal functioning of the infantile organism—the maturation of those functions and capacities which belong to normal human life and make normal reactions possible. All the love the mother can give to the child may not be effective, not only because the infant himself cannot react to it adequately, but also because the mother in turn will not react appropriately if she perceives the child's behavior as inadequate.

The reactions of infants under conditions of stress are not equivalent to behaviorally identical reactions of older persons. It is important to bear this in mind. As regards autism, for example, a normal adult or older child in danger of losing contact with the world may use "withdrawal" as a means of warding off the fear related to this danger. In the adult such a withdrawal reaction may signify intentional aloneness and avoidance of contact. But in younger children, and particularly in abnormal children, we are not dealing with the same phenomenon. The infant, whether normal or abnormal, does not withdraw intentionally. His withdrawal is simply a function of his inability to do anything else, and he perseverates in the withdrawal activity. Kanner's children seemed to behave in this way. In my opinion, the term *autism* should not be applied to behavior of this kind; rather, it should be reserved for intentional withdrawal to avoid contact. The abnormal child does not seem to experience either contact or lack of contact. He will continue a given activity, particularly when he senses achievement of something that has "value" for him, *e.g.*, brings satisfaction by the expression of appreciation and admiration by other people.

My observations lead me seriously to question Mahler's statement to the effect that the autistic child is "most intolerant of direct human contact." He is so intolerant only when he is confronted with demands he cannot fulfill, when he is disturbed in doing what he can do, or forced to do something else.

It would be important to determine whether children who become "psychotic" have specialized endowments and abilities, and whether this is more the case with "autistic" children than with children having "symbiotic" symptom-complexes. Autistic children would presumably feel more at ease in using their capacities; symbiotic children would look more for protection from the outside.

Thus we come to the position that in the "early childhood psychoses" we are dealing with conditions which are understandable as deviations from normal childhood behavior. These conditions are due to defects in development and maturation, and to inadequate behavior of the enviroment. As the influence of these two classes of factors varies, we observe different abnormal conditions. The organism tries to act in such a way as to realize its possibilities, in normal as well as in abnormal conditions. When the child has to live on a primitive level of development his contact with the world is

disturbed. A child may then appear "withdrawn" (autistic), or in an abnormal closeness with the world (in a "symbiotic" relationship). In both reactions self-realization is possible only in a reduced form, in "abnormal behavior." Under these abnormal conditions the psychological survival of the child requires that there be no environmental interference with the limited activities he is able to perform. Performance of these activities protects him against the dangers which the demands of the normal world represent.

As compared with the child of normal mental development, the abnormal child has limited adjustment capacities. The limitations stem from deficiencies of innate reactions and of abstract attitude, and result in various modifications of normal behavior. Development or maturation of innate capacities and the ways the abnormal child can come to terms with the world are adversely affected. The behavior of the mother is of great influence on the development of the symptomatology—she may, protecting the infant, give rise to "symbiotic" behavior, or she may permit the baby to "withdraw." The special abilities—the extraordinary endowments in limited fields that these children often possess—are potent determinants of the developing symptomatology. These special skills, used at the primitive levels beyond which these children cannot operate, bring satisfaction and the feeling of well-being which is connected with all "adequate" activities. In this way the children may enter social contact and develop pseudo-social relationships.

Accordingly, the endowments and how they are used must be carefully evaluated in order to understand the behavior of abnormal children. In clinical appraisals of these children, I am strongly inclined to avoid distinguishing "autistic" and "symbiotic" conditions, because they may be no more than different reactions by which the abnormal organism has come to terms with the world. (The development of normal behavior proceeds according to the same general principles.) I am inclined not to speak of psychoses in this connection, no more than we speak of psychoses in relation to the reaction forms of brain-injured adults.

Our interpretation of these symptom complexes would make understandable the virtual impossibility of effecting improvement by any deep psychotherapy. Such treatment is likely to fail even if one takes the special symptomatology into careful consideration, by avoiding catastrophes as much as possible and attempting—as the main therapeutic goal—to build up a relationship between the child and the environment. Mahler remarks that, "the outlook as to a real cure is bleak." Even if the child cautiously "begins testing of himself as a separate entity . . . the ego remains irreparably warped, narcissistically vulnerable, unstructured or fragmented." We learn that as the children become older they appear less restless, more active, cooperative, seem better adjusted and able to acquire knowledge. This, indeed, only if the environment is so organized (as to demands from the world around and from the people the child has to live with) that catastrophes seldom occur. Although the symptoms simulating psychosis may then diminish that does not mean the condition has really improved. It is characteristic that in the state of so-called improvement the child "constantly needs to feel the support of an understanding adult, preferably the mother or the therapist as mother substitute" (11, p. 302). This description of the improved condition corresponds neatly with the observations we have made of children described as idiots-savants.

REFERENCES

1. Goldstein, K. Concerning rigidity. Character & Personality, **11**: 209–226, 1943.
2. Goldstein, K. The effect of brain damage on the personality. Psychiatry, **15**: 245–260, 1952.
3. Goldstein, K. A further comparison of the Moro reflex and startle pattern. J. Psychol., **6**: 33–42, 1938.

4. GOLDSTEIN, K. *Language and Language Disturbances.* Grune & Stratton, New York, 1948.
5. GOLDSTEIN, K. *The Organism,* Ch. 7. American Book Co., New York, 1939.
6. GOLDSTEIN, K. The significance of the frontal lobes for mental performance. J. Neurol. & Psychopath., **17:** 27–40, 1936.
7. GOLDSTEIN, K. The smiling of the infant and the problem of understanding the "other." J. Psychol., **44:** 175–191, 1957.
8. GOLDSTEIN, K., LANDIS, C., HUNT, A. AND CLARKE, F. M. Moro reflex and startle pattern. Arch. Neurol. & Psychiat., **40:** 322–327, 1938.
9. KANNER, L. Autistic disturbances of affective contact. Nerv. Child, **2:** 217–250, 1943.
10. KANNER, L. *Child Psychiatry,* (2nd ed.). C. C Thomas, Springfield, Ill., 1948.
11. MAHLER, MARGARET S. On child psychosis and schizophrenia: autistic and symbiotic psychoses. Psychoanalyt. Study of the Child, **7:** 286–305, 1952.
12. SCHEERER, M., ROTHMANN, E. AND GOLDSTEIN, K. A case of "Idiot Savant": An experimental study of personality organization. Psychological Monogr., **58:** No. 4, 1945.

AN EXPLORATORY INVESTIGATION OF THE EFFECT OF MEPROBAMATE ON STUTTERING BEHAVIOR

L. M. DI CARLO, PH.D.,[1] JACK KATZ, M.S. AND STANLEY BATKIN, M.D.

Of the many speech impairments which handicap children and adults in the communicative process, few have attracted as much attention as stuttering (10). Indeed, such a vast reservoir of literature, both experimental and theoretical, has accumulated that it would require an individual a lifetime of study to assimilate and evaluate. Stuttering, one of the most common of the functional type of speech disturbance, has been attributed to many causes. Although general agreement does not exist concerning underlying etiological factors, agreement does exist regarding certain aspects of therapy. Most investigators believe that stuttering is a cause of anxiety (1, 11, 19, 21), and that alleviation of this secondary effect should be given first consideration.

Meprobamate, an ataractic agent, has been used successfully in the treatment of patients with psychiatric disorders (2, 3, 9, 15), cerebral palsy (6, 17), muscular disorders (7), rheumatism (18) and anxiety states (13). Meprobamate (Equanil®) acts directly on muscles (5) and the degree of toxicity is low (17). It has been reported that continued ingestion of large dosages of meprobamate can cause physical dependence; however addiction to meprobamate probably will occur in only a very small proportion of persons who receive the drug therapeutically (4). While the relatively few cases in which meprobamate is habit forming should not detract from the general usefulness of the drug, it does place a responsibility on the physician to supervise carefully its administration (14).

[1] The Gordon D. Hoople Hearing and Speech Center, Syracuse University, Syracuse, New York. Thanks are extended to the Wyeth Laboratories for their generosity in supplying both the Equanil and the placebo tablets used in this investigation.

Because of its unique properties, meprobamate suggests itself as a possible agent in reducing stuttering behavior. Recently, meprobamate has been used as an adjunct to the accepted therapy for subjects who stutter (4, 14).

METHOD AND SELECTION

This investigation was designed to investigate the effect of meprobamate on the stuttering behavior of stutterers, and to observe changes, if any, produced in the stuttered moments and in the severity of stuttering.

Thirty stutterers[2], 22 men and eight women, were selected to participate in this study. These individuals had been diagnosed as stutterers on the basis of Johnson's (11) criteria. Their speech was sufficiently deviant to call attention to itself; they had been analyzed as stutterers by individuals in their environment; and they considered themselves stutterers. The ages of the subjects ranged between 15 and 45 years. The mean and median ages were 22.6 and 22 years respectively. All subjects had received therapy for stuttering previous to this investigation. During the investigation all therapy was suspended in order to determine the effect of the meprobamate without therapy.

Each stutterer was seen once each week for a period of six weeks. At the first meeting, the subject was given a 500-word passage which consisted of elementary vocabulary (fourth or fifth grade level). The subject was permitted to become familiar with the passage and then was asked to read it aloud. The reading was recorded

[2] Selected from patients attending the Gordon D. Hoople Hearing and Speech Center, Syracuse University.

and a trained technician monitored the recording level. At the completion of the first reading, the Iowa Scale of Attitude Toward Stuttering (21) was administered. After the preliminary tests were completed, each stutterer was given a neurologic examination.

The ten stutterers in each of three groups were selected on the basis of random sampling and a psychiatric examination.[3] The subjects were assigned numbers from 1 to 30. Those who had numbers 1, 4, 7, 10, 13, 16, 19, 22, 25, and 28 were placed in the meprobamate group; those who had numbers 2, 5, 8, 11, 14, 17, 20, 23, 26, and 29 were placed in the "placebo group"; and those who had numbers 3, 6, 9, 12, 15, 18, 21, 24, 27, and 30 were placed in the "no medication" group.

Ten of the 30 subjects were given meprobamate (bottle of 100 tablets); one-half tablet to be taken three times a day (600 mg.) for the first week; three tablets a day for the second week; four tablets a day for the third week; and five tablets a day for the fourth week. If the patient experienced any side effects from the medication, the dose was to be reduced to the previous level at which side effects were not observed. Ten of the 20 remaining subjects were given placebo tablets with instructions identical to those given to the subjects for whom meprobamate was prescribed. Medication was not prescribed for the remaining ten subjects.

Reading and recording of the 500-word passage was completed once each week. At the end of the second visit, the Taylor Manifest Anxiety Scale Test (20) was administered to the subjects. At the end of the last visit, both the Taylor Manifest Anxiety Scale Test and the Iowa Scale of Attitude Toward Stuttering were administered, and a neurological examination was conducted.

The recording of each reading was replayed by the investigator who indicated the stuttered moments by drawing a line through the word on a printed form. The following criteria were used in determining a stuttered moment: repetition of a word or syllable, prolongation of a word or syllable, unnecessary pause or hesitation before or in the middle of a word, insertion of an extra word or sound before or in the middle of a word, substitution of another word or words for the specified word, and omission of a word.

The reliability of the experimenter was 86.7 per cent, as determined by comparison with the results of three qualified speech therapists who were asked to rate the same recordings. Neither the experimenter nor the three speech therapists were aware of the experimental group assignments of the subjects.

RESULTS AND DISCUSSION

The means, standard deviations, and *F* values of stuttered moments for the three groups on six different readings are presented in Table 1.

For the meprobamate group, there was a decrease in stuttered moments from the second reading to the sixth. The variance indicated wider scatter of performance and decrease in the standard deviation between the first and the five following readings.

In the placebo group, the first reading contained fewer stuttered moments. Of the remaining five readings, the fourth reading represented the fewest stuttered moments. Variance in this group also was large, and the standard deviation of the last five readings showed an increase over the first.

In the group for which medication was not prescribed, the mean for each reading showed an increase in the number of stuttered moments from the first to the sixth reading. The standard deviation was largest for the sixth reading.

[3] Conducted by Dr. Richard S. Phillips, Department of Psychiatry, New York State, State University, Upstate Medical School. The authors acknowledge with thanks Dr. Phillips' participation.

TABLE 1

Means, Standard Deviations, and F Values of the Number of Stuttered Moments on a Five Hundred Word Passage on Six Different Readings at One-Week Intervals by Individuals Assigned Meprobamate, Placebo, or no Medication

	Reading					
	I	II	III	IV	V	VI
Meprobamate						
$\bar{x}$	86.7	62.2	65.3	64.0	65.3	56.6
σ	121.34	74.46	73.69	85.94	77.36	68.64
Placebo						
$\bar{x}$	75.3	90.0	88.8	80.6	84.8	86.8
σ	74.8	79.2	78.8	66.2	71.2	79.5
No Medication						
$\bar{x}$	56.4	64.3	64.0	66.5	75.6	77.3
σ	54.14	59.29	61.64	61.90	75.37	79.57
*F value**						

1. For the three groups on reading I (before medication) F value = .27
2. For the three groups between readings I and VI (medication administered after reading I) F value = 2.81

* $F_{.01} = 5.49$
$F_{.05} = 3.35$
$F_{.10} = 2.51$

The F value for the three groups on reading I and the F value of the difference scores between the first and the sixth reading are also presented in Table 1. The obtained F value of .27 allows of the hypothesis that the subjects come from the same or similar populations since an F value of 3.35 is required for significance at the 0.05 level of confidence. An F value of 2.81 revealed that the means for the difference score were not statistically significant at the 0.05 level, but were significant at less than the 0.10 level of confidence. Analysis of the data presented in Table 1 reveals a difference in means that may be of some practical value; that is, although differences were not statistically significant, a decided trend is apparent. (Frequently, when the variability is great among samples, the difference may not be significant, while numerically the difference may be sufficiently large to be important operationally in implementing a certain approach.) For the meprobamate group, there was a decrease in the number of stuttered moments from 86.7 to 56.6, a difference of 30 stuttered moments. For the placebo group, there was a mean difference from 75.3 to 86.8, a difference of −11.5, indicating an increase in the number of stuttered moments. The mean difference for the group for which medication was not prescribed was from 56.4 to 77.3 or −20.9, indicating an increase in the number of stuttered moments.

The subjective expression of the effect of medication on speech and relaxation by the meprobamate and placebo groups was obtained through interview. Of the ten subjects in the meprobamate group, nine reported they were more relaxed; one reported no improvement. In the placebo group, two subjects believed the medication had relaxed them; eight expressed no change in their anxiety feelings. Six stutterers in the meprobamate group believed that the medication had been beneficial to their speech production; four expressed no improvement, but no deterioration. Two subjects in the placebo group believed that the medication had been beneficial, five believed that their speech had deteriorated, and one was unable to make a judgment.

There was no statistically significant difference between the performances on the attitude scale on either the first or sixth visits for the meprobamate, placebo, no medication, or combined groups.

CONCLUSIONS

Ten stutterers given 600 mg. of meprobamate per day for the first week, 1,200 mg. per day for the second week, 1,600 mg. per day the third week, and 2,000 mg. per day the fourth week showed a reduction in the mean number of stuttered moments. This reduction, while not achieving statistical significance, did show a definite trend and was significant at the .10 level of confidence for the group that received meprobamate. Non-parametric statistics revealed a statistically significant amount of pro-

gressive success with each trial for this group. Their own subjective evaluations confirmed the findings. On the basis of these results, further study is indicated.

REFERENCES

1. Blanton, S. Stuttering. J.A.M.A., **160**: 1472, 1956.
2. Borrus, S. C. Study of Miltown (2-Methyl-2-n-Propyl-1,3-Propanediol Dicarbamate) on psychiatric states. J.A.M.A., **157**: 1596–1598, 1955.
3. Bower, W. H. Meprobamate in senile psychosis. Ann. New York Acad. Sci., **67**: 801–809, 1957.
4. Essig, C. F. and Ainslie, J. D. Addiction to meprobamate. J.A.M.A., **164**: 1382, 1957.
5. Gerard, R. W. Drugs for the soul; the rise of psychopharmacology. Science, **125**: 201–203, 1957.
6. Gillette, H. E. The effect of meprobamate on cerebral palsy. Ann. New York Acad. Sci., **67**: 859–872, 1957.
7. Gillette, H. E. Relaxant effects of meprobamate in disabilities resulting from musculoskeletal and central nervous system disorders; clinical observations of fifty-five cases. Internat. Rec. Med. & Gen. Pract. Clin., **169**: 453–568, 1956.
8. Holliday, A. R. The effect of meprobamate on stuttering. Paper read before the King County Medical Society, April 7, 1958.
9. Hollister, L. E., Elkins, H., Hiller, E. G. and St. Pierre, R. Meprobamate in chronic psychiatric patients. Ann. New York Acad. Sci., **67**: 789–798, 1957.
10. Johnson, W. *Stuttering in Children and Adults; Thirty Years of Research at the University of Iowa*. Univ. of Minnesota Press, Minneapolis, 1955.
11. Johnson, W., and others. *Speech Handicapped School Children*. Rev. ed. Harper, New York, 1956.
12. Johnson, W., Darley, F. L. and Spriestersbach, D. C. *Diagnostic Manual in Speech Correction; A Professional Training Workbook*. Harper, New York, 1952.
13. Lamphier, T. A. Drug addiction. J.A.M.A., **163**: 68, 1957.
14. Lemere, F. Habit-forming properties of meprobamate. A.M.A. Arch. Neurol. & Psychiat., **76**: 205–206, 1956.
15. Litchfield, H. R. Clinical evaluation of meprobamate in disturbed and prepsychotic children. Ann. New York Acad. Sci., **67**: 828–831, 1957.
16. Maxwell, R. D. H. and Patterson, J. W. Meprobamate in the treatment of stuttering. Brit. M. J., **1**: 873–874, 1958.
17. Perlstein, M. A. Use of meprobamate (Miltown) in convulsive and related disorders. J.A.M.A., **161**: 1040–1044, 1956.
18. Smith, R. T. The use of meprobamate and other muscle relaxants in muscle spasm due to rheumatic conditions. Ann. New York Acad. Sci., **67**: 839–852, 1957.
19. Solomon, M. Stuttering as an emotional and personality disorder ... A socio-psychological approach. In Hahn, E. F. *Stuttering: Significant Theories and Therapies*. Stanford Univ. Press, Stanford, 1943.
20. Taylor, J. A. A personality of manifest anxiety. J. Abnorm. & Social Psychol., **48**: 285–290, 1953.
21. Van Riper, C. *Speech Corrections; Principles and Methods*. 3rd ed. Prentice-Hall, Englewood Cliffs, New Jersey, 1954.

BRIEF COMMUNICATION

THE EFFECT OF VARIOUS THERAPIES UPON FECAL INCONTINENCE IN CHRONIC SCHIZOPHRENIC PATIENTS

NORBERT FREEDMAN, PH.D.,[1] LEON WARSHAW, PH.D.,[2] DAVID M. ENGELHARDT, M.D.,[1] IRVING J. BLUMENTHAL, M.D.[2] AND LEON D. HANKOFF, M.D.[1]

In the present study, three different treatment strategies were successively applied to a group of regressed schizophrenic patients. The major outcome criterion was incidence of fecal incontinence. This criterion has the advantage of being objective in that it is quantifiable and yields ready observer agreement. The three treatment strategies were: 1) group play therapy only; 2) group play therapy with psychopharmacological agents (phenothiazine and amphetamine derivatives); and 3) group play therapy with placebo. It was hypothesized that all the therapies would inhibit soiling and that the effectiveness would increase with each treatment factor added to play therapy, that is, with the addition of placebo and active medication.

It is to be noted that our patients were not incontinent on a neurogenic basis. The act of soiling in these patients may be regarded as a schizophrenic symptom, perhaps a communication, and a psychotic defense mechanism. In this light, we have asked: What changes might occur along with decreased soiling? It is reasonable to expect other changes if the schizophrenic patient alters his mode of functioning.

This report then deals with 1) the effect of various treatment regimens upon the incidence of fecal incontinence; and 2) in a more exploratory manner, the alterations in defensive structure concomitant with changes in soiling behavior.

PROCEDURE

Patients. Twelve chronic schizophrenic patients were selected from a single ward at Northport Veterans Administration Hospital. All patients had a history of hospitalization of several years, evidence of fecal incontinence during the six months prior to the investigation, and signs of severe regression. In addition to incontinence there were frequent instances of assaultiveness and destructiveness, poor verbal communication to the point of muteness, and regressive posture. Patients with neurological disturbances, including those who had undergone a lobotomy, were excluded. CNS lesions were ruled out by means of history and neurological examination, including electroencephalogram.

Treatment Procedures. 1) The play therapy was conducted in two groups of six patients, each meeting twice a week for six months, the duration of the experiment. The

[1] The Psychopharmacological Research Unit, Department of Psychiatry, State University of New York, Downstate Medical Center, Brooklyn, New York. This study was supported in part by grants from the National Institute of Mental Health, U.S. Public Health Service (MY 1983), and Wyeth Laboratories, Radnor, Pennsylvania, to the Research Foundation, State University of New York. The promazine used in this study was supplied as Sparine and the mephentermine (N-methylphenyl-tertiary-butylamine) as Wyamine elixir by Wyeth Laboratories. The authors wish to express their appreciation to Nursing Assistants Alexander Beato and Earnest Woodall and Occupational Therapist Geraldine Cline, all of the Veterans Administration Hospital, Northport, and Walter Ritter, State University of New York.

[2] Veterans Administration Hospital, Northport, New York. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

play therapist (ward psychologist) was assisted by a nursing assistant and an occupational therapist. A variety of toys was available to the patients. The patients generally played games (Ping-pong, pegboard) but they also used clay and finger paint. There was little verbal communication among patients. 2) Drug treatment consisted of the addition to play therapy of 100 mgm. of promazine q.i.d. in capsules after a five-day build-up period and 12½ mgm. of mephentermine in elixir b.i.d. 3) Placebo treatment consisted of the addition to play therapy of capsules (to simulate promazine), and a syrup (to simulate mephentermine elixir). This study was "double-blind"; neither the patients nor the staff in charge of patient evaluation, *i.e.* therapist or aides, knew when the patient was receiving the active medication.

Treatment Sequence. The duration of the project was six months plus a two-month baseline observation period prior to the start of treatment. Each patient received each treatment for two months. Treatments were rotated in three different sequences: 1) play therapy only, placebo, drug; 2) placebo, drug, play therapy only; and 3) drug, play therapy only, placebo. The 12 patients were divided into three sequence groups of four patients each.

Data Sources. Two types of data were collected. Soiling frequency was determined by a daily entry on a chart retained on the ward. When a patient suffered from diarrhea or was temporarily absent from the ward, these days were eliminated from the count. Soiling frequencies were based on a 60-day observation period for each treatment regimen, prorated for absences.

The second source of data concerned the patients' ward behavior in areas other than soiling. Items 41–62 of the Lorr Scale, dealing exclusively with ward behavior, were used (1). Ratings were made by nursing assistants who had long acquaintance with the patients and ample opportunity for observation.

TABLE 1

Comparison of Soiling Frequencies among Conditions of Observation: t-Values for Differences between Means

	Baseline	Play Therapy	Placebo	Drug
Baseline	X	2.29*	2.44*	2.95†
Play Therapy		X	.48	.61
Placebo			X	.31
Drug				X

* $P < .05$ level of confidence, 11 d.f. 0.05
† $P < .02$ level of confidence, 11 d.f. 0.02

RESULTS

Changes in Soiling Frequency. The incidence of soiling per patient was prorated for each 60-day observation period. Total frequencies for all 12 patients were as follows: baseline, 115 instances; play therapy only, 71; placebo, 57; and drug, 51. Thus, incidence of soiling frequency showed a progressive decline from baseline to play therapy only to placebo to drug. All three forms of treatment result in a statistically significant decline of soiling relative to the pretreatment baseline, as shown by the *t*-values of Table 1.

On the basis of soiling frequencies alone, none of the three treatments appear to be significantly differentiated from one another. However, the addition of placebo and then drug seems to result in a cumulatively greater effectiveness. (Of four patients continued on drug alone, after the conclusion of the experiment, only two maintained the lowered incidence of soiling.)

Considering soiling from the point of view of variability, standard deviations of 8.00, 7.23, and 4.80 for play therapy, placebo, and drug, respectively, were found. Thus, the standard deviation of soiling frequency for patients on active drugs is significantly lower than under the conditions of play therapy only ($F = 2.79$; $n_1 = 11$, $n_2 = 11$; $F_{.05} = 2.82$). Drug treatment also appears to have lower variability than placebo, but it fails to reach a statistically significant level ($F = 2.27$; $n_1 = 11$; $n_2 = 11$). The

findings indicate that while all treatment approaches resulted in less soiling, promazine-mephentermine contributed to this effect more uniformly. Length of treatment *per se* did not reliably affect soiling frequency. The decrease in soiling frequency relative to the baseline period fluctuated as follows: 1) first two months, 71 less instances (62 per cent); 2) second two months, 27 less instances (24 per cent); and 3) third two months, 61 less instances (53 per cent).

Changes in Ward Behavior. Of the 22 rating scale items employed, four differentiated significantly between baseline and treatment condition. The findings in Table 2 indicate that relative to the baseline, the patients were rated during the treatment period as less assaultive and threatening, but manifesting more obscenity, irritability, and self-talking. These changes were not specific to any treatment regimen. In comparing behavior ratings among the three treatment conditions, none of the mean ratings showed a significant difference from the others.

Correlates of Changes in Soiling. In order to study the correlates of soiling change, we chose as our observation period the condition under which the largest decline in soiling behavior had been observed, namely, drug treatment. Under the administration of promazine-mephentermine, ten of 12 patients showed a decline in soiling behavior. Among these ten patients eight became less assaultive or threatening, eight became more profane and obscene, six showed a greater tendency to talk to themselves, and seven showed greater irritability.

TABLE 2

Mean Ward Behavior Ratings according to Conditions of Observation

Rating Scale Item	Conditions of Observation			
	Baseline	Play Therapy	Placebo	Drug
#43 Profanity & obscenity	1.47	1.67	1.77‡	1.72‡
#44 Talks to self	1.68	1.93†	1.91*	1.92*
#47 Irritable	1.79	2.07‡	2.01	2.01
#60 Assaultive and threatening	1.29	1.00‡	1.01‡	1.00‡

Comparing baseline vs. treatment conditions:
* $P < 0.05$; $t_{0.05} = 2.20$; 11 d.f.
† $P < 0.02$; $t_{0.02} = 2.72$; 11 d.f.
‡ $P < 0.01$; $t_{0.01} = 3.10$; 11 d.f.

CONCLUSIONS

1. Incidence of fecal incontinence was used as an objective criterion in evaluating three treatment strategies successively applied to 12 regressed schizophrenic patients. The data supported the hypothesis that all treatment approaches reduce the incidence of incontinence and in a predicted order. In particular, the addition of promazine-mephentermine to group play therapy was the condition leading to the greatest inhibition of soiling and the most uniform response.

2. Reduction in soiling was associated with changes in the manifestations of the patients' defenses. As the patient controlled fecal incontinence, assaultiveness declined but there was an emergence of autistic behavior in the form of profanity, obscenity, and self-talking.

3. The changes may be interpreted as signifying a partial surrender of the regressive state. We witnessed a replacing of direct, instinctual, and motoric expression by indirect, more neutralized, and symbolic expression of the psychotic state.

4. Time of treatment exposure *per se* did not reduce the effectiveness of treatment. This finding may be attributed to the alteration of the regimen every two months. From the viewpoint of ward management, the frequent and regular rotation of treatment approaches may have merit in the control of regressive behavior.

5. On theoretical grounds and on the basis of the literature (2), we regard the group therapy situation as the essential condition for reducing soiling. We interpret the play therapy situation as facilitating communication with the environment,

thereby controlling psychotic acting-out. The drug effect may be seen as accentuating the outcome of play therapy, or, more generally, as influencing the quantitative aspects of behavior. Direction of behavior is probably determined by the social milieu and the set of the individual.

REFERENCES

1. Lorr, M. A multidimensional scale for rating psychiatric patients. Veterans Administration Technical Bulletin, TB 10-507, November, 1955.
2. Schwartz, M. S. and Stanton, A. H. A social psychological study of incontinence. Psychiat., **13**: 399–416, 1950.

WHITE, ROBERT W. *Lives in Progress: A Study of the Natural Growth of Personality.* Dryden Press, New York, 1952. ix + 376 pp. $3.00

The author of this book has become well-known both for his theoretical position of conservative eclecticism and his ability to explore in a clear, readable style material which can readily appear dull and pedantic. In this, his latest book on the psychology of normal personality, he presents introductory material to a field in which he is experienced and capable, and in a manner which the novice will understand, enjoy and accept as reasonable.

The book reflects the author's unwillingness to consider a single causal force as being the prime factor in personality development and change. Thus, weight is given to a variety of factors and the individual personality is presented as a product of their interaction. The reader is reminded of the importance of three formative influences: the innate, biological weakness, abilities and aptitudes; the dynamics of pertinent interpersonal relationships; and the cultural milieu with its values, demands, and realistic limitations. As is suggested from the extent of the undertaking, none of these is treated exhaustively. Instead, the reader is given the theoretical bases for each in highly simplified form. Suggestions for more detailed reading are given at the end of each section, to provide for curiosity whetted by the text.

Three case histories are presented at considerable length, to illustrate and make more concrete the sometimes difficult theoretical considerations. The initial case material on these young, middle-class adults was collected over a period of several months, using a variety of clinical and interview techniques. Later, follow-up material was obtained through intensive interviews. Although the author is aware of the lack of depth which his method of evaluation permits, the findings presented are remarkable for their breadth and clarity. To the extent that the purpose of supplying useful material for illustration and comparison is well served by biographical material, this method of exposition may be considered successful. However, so great a proportion of the book is taken in presenting illustrative material, that the goal of discussing personality in general is often lost in multitudinous specificity.

This volume stresses a point which is often overlooked: the potential of the mature personality for change as a result of ongoing experience. Many writers in this area draw inferences from their work with neurotic adults, people who have not been able to benefit from new relationships. It is easy to forget that this is not necessarily so, that significant personality changes can indeed occur in the adult. White gives a clear, documented description of the manner in which personality, as a nonstatic function, can both act upon and be influenced by environmental conditions. If the book could be weighed for its successes and weaknesses, the treatment of this theme alone would be sufficient to tip the scales in its favor.

H. Aronson

Proceedings of Four Conferences of Parapsychological Studies. Parapsychology Foundation, New York, 1957. xiv + 180 pp. $3.00

ZORAB, GEORGE. *Bibliography of Parapsychology.* Parapsychology Foundation, New York, 1957. 127 pp. $3.75

In the two-year period from 1954 to 1956, the Parapsychology Foundation sponsored four international conferences dealing with the philosophical interpretation of parapsychological phenomena, unorthodox healing,

spontaneous parapsychological phenomena, and the relationship between psychology and parapsychology. The first volume listed above presents brief abstracts (most of them two or three pages in length) of the more than 50 papers read at these conferences by participants from Western Europe, Canada, and the United States. Such familiar figures as J. B. Rhine and Gardner Murphy of this country (the latter is General Research Consultant of the Parapsychology Foundation), and H. H. Price and Robert H. Thouless of Great Britain took part in these conferences. The participants from the European Continent are presumably equally prominent, though not so well-known here.

Readers of this journal will probably find the material from the conferences on unorthodox healing and the relationship between psychology and parapsychology of greatest interest. Included are papers on parapsychological diagnostics and therapy, the Rorschach method in unorthodox healing, the psychoanalytical approach to psi phenomena, bilocation phenomena in neuropathology, and other equally provocative topics. The brevity of the summarized papers precludes the presentation of much substantive material, but the reader does obtain some idea of the breadth of interests of contemporary parapsychologists, and of their ambitious plans for future study and research.

Those who are motivated to read further in the field of parapsychology will find helpful the *Bibliography of Parapsychology* compiled by George Zorab under the auspices of the First International Conference of Parapsychological Studies. Mr. Zorab is Honorary Secretary of the Netherlands Society for Psychical Reserach (the Hague) and Chairman of the International Committee for the Study of Spontaneous Paranormal Phenomena. His is the first bibliography dealing with parapsychology ever to be published. Hundreds of selected references from the American and European literature are listed chronologically under each of 10 headings: Mental Phenomena, *e.g.*, telepathy and clairvoyance; Physical Phenomena, *e.g.*, materialization and levitation; Haunting Phenomena; Quantitative Experiments, etc. Under the category of Parapsychology and the Sciences and Disciplines, ten pages are devoted to books and papers in the field of medicine, including sections on psychoanalysis, psychiatry, and physiology; and an additional six pages list publications in psychology. The bibliography is not annotated, but it is accompanied by useful indexes of authors and subjects.

Those who accept parapsychology and many of those who have not yet made up their minds about it will want to read the proceedings of the four conferences; they will be grateful for Zorab's bibliography as a point of departure for pursuing topics of special interest. Those who have closed the door on parapsychology will probably not have it forced open by these two volumes.

A. B. Silverstein

WIKLER, ABRAHAM. *The Relation of Psychiatry to Pharmacology.* Williams and Wilkins Co., Baltimore, 1957. vii + 322 pp. $4.00

Nothing is more needed at the present time than a carefully integrated logical analysis of the data and concepts involved in the area of neuro- or psycho-pharmacology. New drugs purporting to accomplish behavioral miracles keep appearing, enthusiasms periodically wax and wane and patients come and go—frequently to return. This entire area of both investigation and therapy is fraught with unanswered questions at all levels. What can or should drugs be expected to do? What do they actually do; why and how? Is there any rational way, *i.e.* any series of logical steps by which drug action can be analyzed and predicted? What relation does this problem bear to the basic problems of existing limitations of physiological and chemical explanations in psychiatry? These and a host of other im-

portant, relevant questions must be answered if we are to avoid being trapped by the "forward look" in modern witch-doctoring.

Dr. Wikler lays no claim to having set out to either ask or answer all such questions. He does attempt, and successfully, to examine some current facts and theories in psychiatry and pharmacology in an effort to "survey the problems which will have to be resolved in the future." He has, consequently, reviewed the literature from 1930–1955 dealing with the effects of drugs used in psychiatry in the treatment or investigation of the so-called functional behavior disorders. Even within these limits this was a monumental task, and only a selected portion of the available material could be included. (Despite this it should be pointed out that the bibliography contains 889 references). The author states this quite plainly, and it can only be hoped that he will extend his analysis in future reviews.

The material is arranged in two major sections:

1). The effects of drugs on human behavior; and

2). Theories and mechanisms of drug actions.

The drugs reviewed include insulin, carbon dioxide, barbiturates and other anesthetics, amphetamine and methamphetamine, pipadrol, chlorpromazine, reserpine, meprobamate, azacyclonol, d-lysergic acid diethylamide and mescaline. Epinephrine, norepinephrine, acetylcholine and methacholine, pituitary-adrenal hormones, morphine and other potent analgesics have been considered only incidentally in connection with the actions of other drugs. Addiction problems have been reviewed by the author in previous publications. All the material presented is well documented and a good deal of it critically appraised. Dr. Wikler appears to be aware of both the problems of meaning and definition involved, although he did not feel this volume to be the proper place to go too deeply into their implications and the consequences of blindness to them from which both investigation and therapy suffer so severely. There is no question that this review should be carefully studied by everyone concerned with human behavior, mental disease and all the related questions raised by their consideration.

This reviewer would carp at the moment only with Dr. Wikler's neglect to discuss certain molecular theories relative to the selective action of various substances in the nervous system, as well as their relationship to intracellular energy mechanisms. Within the last few years physico- and biochemical data and theory of this nature have been molded into a working construct or model by which action of various substances can be tested. Such a construct presents the possibility of predicting neuronal responses to particular molecular structures, and consequently a more rational approach to drug design and therapy as well as to the broad concepts of disease. It is unfortunate that this aspect of current thinking escaped the author of this, in general, most capable and valuable contribution.

Robert G. Grenell

GLANZ, E. C. AND WALSTON, E. B. *An Introduction to Personal Adjustment.* Allyn and Bacon, Boston, 1958. xv + 348 pp. $5.75

In their foreword, the authors state that, "*An Introduction to Personal Adjustment* is constructed as a textbook and as a student handbook for a basic and integrative personal experience within a total educational process" (p. viii). Finding himself to a degree baffled by this sentence, the reviewer then searched the foreword at length to try to discover for what purposes this book was written. Three major aims could be identified.

First, it is intended as an introduction to the science of psychology, and designed for freshman courses in that subject. Second, it is recommended for courses in orientation

to college. Third, it is suggested for use in guidance and counseling. It is unfortunate that data were not presented to show how useful it is for any or all of these purposes. If the book really serves all of them, it is surely an achievement of the first rank. In the absence of data about its effectiveness, however, the reviewer finds himself left in a position of extreme skepticism.

One of the keystones of the mental health movement is the assumption that an informed and enlightened public can have the same good effects on mental health that an informed public has had on physical health. The public health movement has been one of the most significant social forces of the past century, and it is just getting into high gear. There is hope that the mental health movement can be similarly successful.

In order for this to happen, however, essential information and attitudes must be judiciously and forcefully presented to large segments of the public. College students, as future leaders in their communities, certainly seem like a fertile ground for this information. They need to know about human behavior (modern psychology); they need to be able to be able to make use of their talents in college (orientation); if their knowledge is to serve its best purposes, they should be helped to achieve social maturity, personal effectiveness, and reasonable adjustment (mental health).

Glanz, Walston, and their colleagues (a number of others participated in the preparation of several sections of the book) seem to have sensed this need and have apparently tried to meet it. The many shortcomings of their book might conceivably be attributed to its being a pioneering attempt. To take this tack, however, would mean failing to face up to the very serious issues involved.

The book is intended to be an introduction to modern psychology, and is recommended as a text for the first or introductory course. While the authors suggest that the book be supplemented by certain outside readings, the reviewer's experience leads him to doubt that this would be a successful substitute for presenting a reasonably complete picture of modern psychology within the covers of the book. In other words, if the writers are going to recommend this as an introduction to psychology, they have a clear responsibility to introduce the student to *all* of psychology (within the normal limits imposed by any text).

A brief history of psychology and its fields of activity is presented in the first chapter. The authors' conception of psychology's development and major problems is exceedingly primitive and misleading. Animal experimentation is referred to as a "substitute," seemingly in complete unawareness of the goals of behavior theorists. The impression is created that various schools of psychology arose *after* the development of behaviorism. One of Freud's alleged contributions to psychology is listed as design (presumably experimental), a topic about which Freud was virtually totally uninterested. Finally, psychology is divided into three areas of concern: experimental or scientific, applied, and clinical. This, to most members of the profession, is a curious division indeed.

A few examples will illustrate the problems to be faced by anyone attempting to use this book as an introduction to psychology. The authors are apparently complete[illegible] committed to self-concept theory as [illegible]ve heart of personality functioning. Ignorant of the Nebraska symposia on motivation, they equate drive and need. Later on, in discussing learning, they opine that learning *normally* (sic) involves a change in behavior. They refer to the theoretical paper on occupational choice by Blau *et al.* as a *study*. The reviewer, who was one of the developers of that theory, wonders what must be the authors' conception of research.

Except for a few passing comments about physiological needs and the uncertain effects of heredity on behavior, the authors leave untouched the entire literature of physio-

logical psychology. Perception and sensation are likewise missing. Descriptive statistics are given short shrift, and the student is given no information about statistical inference. The notion that psychology is an experimental science is alleged but not demonstrated by reference to the literature of research. Social psychology may be seen, if one looks hard enough, in terms of adjustment to groups, but the student would get no notion of the range and depth of research in this field.

Even the areas included leave much to be desired. Individual differences as a topic hardly gets past the personal equation. There is a brief discussion of tests, but there is nothing worth the name of measurement theory. Learning presents the various modes —trial and error, conditioning, and association—as theories.

This cataloguing could go on *ad infinitum*. Suffice it to say that, considered as an introduction to psychology, this book is totally unacceptable.

The second stated purpose of this book is as an orientation to college. The authors' assumption is, apparently, that a knowledge of psychology will permit the student to understand himself vis-a-vis the collegiate environment and thereby adjust to it. In the later chapters, the authors lead the student through a kind of "self-analysis." They wisely recommend that professional counseling and guidance be employed in conjunction with this. What they outline is fairly traditional counseling procedure. It is an open question whether having this book would help students progress better in either individual or group counseling. The authors imply that it would; the reviewer is unconvinced.

There are other books available better designed to help the student to learn to study effectively, one of the major problems of adjustment to college. These others are somewhat more modest in their goals, tending to deal almost exclusively with study methods.

The third purpose of this book has to do with helping students to achieve better self-understanding and presumably better mental health. Again, it is recommended that professional assistance be provided as the student works at his "self-analysis." Chapter 13, "Process of Self-Analysis," is intended to guide the student through this difficult process. He also has at his disposal a workbook, case studies, self-analysis essays, an autobiographical assignment sheet, and an occupational information check sheet, all these included in the appendices. As the questions and topics are stated, they omit so many areas of importance that it is difficult to see how the student would learn very much of significance about himself. And if he is engaged in counseling with a professional, it is unlikely that the book would add anything of real value.

The rapidly expanding and changing field of psychology is always in need of good introductory textbooks. This does not seem to be one such. As more and more students flood colleges and universities, aids to student orientation are urgently needed. Again, this is not the book. If the mental health movement is to make significant progress, books for laymen need to be written that convey the essential facts and principles of psychology and psychiatry. In the opinion of the reviewer the volume is deficient here as well.

It is quite possible that the authors and their colleagues, employing this book along with outside readings and group and individual counseling, can and do attain the goals they have described. The reviewer doubts very much that this book contributes significantly to this enterprise. In the hands of other teachers, perhaps less motivated or prepared to provide the kinds of other experiences necessary, this could be a dangerous book. In the hands of an unsophisticated student, one without access to professional help, the dangers seem to be very great indeed.

It is regrettable that the book has so

many deficiencies. The authors' basic ideas and goals are good. Their concerns are shared by many as they should be. It may be that, in trying to do too much, they accomplished too little. If so, they are not the first to fall into this trap, and they will probably not be the last.

John W. Gustad

MENNINGER, KARL. *Theory of Psychoanalytic Technique.* Basic Books, Inc., New York, 1958. 206 pp. $4.75

This valuable book reflects the author's broad experience as educator, scientist, clinical psychiatrist, and psychoanalyst. Although its contents were originally directed to candidates in the Topeka Psychoanalytic Institute, it is relevant to the theory and practice of psychotherapy in general, and I consider it recommended reading for psychiatric residents. Menninger's concern with the "two-party contract" of psychoanalysis encompasses many of the elements to which the socio-cultural "schools" of therapy attach almost exclusive importance. It may be worth noting, therefore, that his contribution falls clearly within the mainstream of Freudian thought. He carefully delineates the differences, as he sees them, between psychoanalysis and other forms of psychological treatment. Furthermore, his consistent regard for the unique aspects of the psychoanalytic situation and his careful attention to historical perspective help to define its usefulness as a research method.

Long experience and intimate familiarity with his subject permit Menninger to write not only with authority, but with a refreshingly salty tang. His footnote (p. 161) on the influence of analysts' vacation habits on the termination of analysis is an authentic pearl, and the book is laced with amusing and useful observations of the seasoned practitioner variety. Its theoretical heart is probably contained in his concept of the patients' regression in the context of the various frustrations inherent in the analytic situation. Preparation for an elaboration upon this concept are contained in the major sections of the book: the contract (the "two-party transaction"); the regression; transference and countertransference; resistance; interpretation and other intervention; and, the termination of the contract ("the separation of the two parties").

Menninger's failure to come up with significantly new answers to questions about the nature and mechanisms of analytic change does not detract from the value of his presentation. He clarifies many issues, provides a more precise conceptual framework in which to view psychoanalytic data, and identifies problem areas for research and therapy. Yet, when he writes of more theoretical, in contrast to clinical matters, this reviewer, at least, senses a certain frustration, a struggle to achieve new concepts which cannot quite be accomplished. The introductory sections gave me the feeling that he might be going in the direction of some combination of learning theory, social science, and classical analysis. In later chapters, however, he seems more influenced by Ferenczi. His final statement does not refer to scientific propositions in the ordinary sense, but is a statement of faith and of personal philosophy phrased as a generalization: "There is thus an implicit philosophy and ethic in the psychoanalytic experience . . . it is implicit that love is the greatest thing in the world . . . that true love suffereth long and is kind, envieth not, is not puffed up, seeketh not its own (but the welfare of others), and rejoiceth not in inequity but in the truth."

In the light of this statement we note with particular interest the author's idea, presented in the preface, that the greatest good for the most people will come from "the application of the principles and knowledge gained from the science of psychoanalysis rather than upon its therapeutic applications in particular instances." He recommends that this "intensive post-academic education" be made possible for all those

who teach psychiatry and the social sciences: "I think it is more important for them to get a new concept of themselves, of human beings, and of the world so as better to guide their students than for a similar number of sufferers to be relieved of their symptoms."

Eugene B. Brody

SMITH, KLINE AND FRENCH LABORATORIES STAFF, EDS. *Trifluoperazine: Clinical and Pharmacological Aspects.* Lea and Febiger, Philadelphia, 1958. v + 215 pp. $3.50

This monograph contains a collection of 25 papers on a new phenothiazine tranquilizer (Stelazine) introduced by the Smith, Kline & French Laboratories and relate to the pre-clinical investigations which are divided into five sections. These are: Psychopharmacology, Pharmacology and Chemistry (2 papers); Functional Psychoses (10 papers); Brain Disorders—Mental Deficiency (3 papers); Psychoneuroses and Personality Disorders (3 papers); and Extrapyramidal symptoms and other side effects (3 papers).

In the section on psychopharmacology, pharmacology and chemistry the evaluation of some of the pharmacologic properties of the drug in animals are described. The techniques used for study were the conditioned avoidance response, spontaneous motor activity, cataleptic effect, analgesia, barbiturate potentiation, cardiovascular activity, and toxicity studies. Psychophysiological testing in human subjects exposed to one dose of the drug is reported utilizing such procedures as critical flicker fusion frequency, after-image disappearance levels, tapping reaction time, hand steadiness, digit span, digit symbol substitution, cancellation, spiral after-effect, verbal fluency and body sway tests of suggestibility.

The papers on the functional psychoses are primarily documentary in character, relating the clinical experiences, response, dosage levels and complications. A study reports no contraindication in utilizing trifluoperazine in association with the administration of electroconvulsive therapy. Apparently one-half to one-third of the acute and chronic psychotic patients treated indicated some degree of improvement. The papers on brain disorders relates to its use in treating the disturbed mental defective, with good results reported in the treatment of the hyperactive and disturbed mental defective patient.

The section on psychoneuroses and personality disorders is extremely brief but the warning was issued that because of the drug's potency and the high incidence of extrapyramidal reactions it must be employed carefully. It was felt the drug should not be prescribed for hysterics, obsessive-compulsive and anxiety neurotics who have a low tolerance for discomfort and react adversely to the neurological effects. A trial on alcoholics indicates that in low dosages it appeared to be a safe drug for use in the ambulatory alcoholics.

Particularly welcome is a very well done presentation on extrapyramidal symptoms and other side effects. Data are tabulated in a brief and pertinent fashion; when such symptomatology might occur, their significance and management.

The authors of this collection of papers have had extensive experience with drug therapy, bringing a sophisticated approach to their subject. They present a carefully assembled compendium of do's and don'ts to help others use this new drug. The data presented indicates that trifluoperazine is certainly a potent phenothiazine tranquilizer, dosage-wise, and is associated with a higher incidence and earlier onset of a group of dyskinetic neurological complications. These factors emphasize one of the primary goals of this monograph, namely, the prompt education of physicians in the technique of administering the drug. Its importance and status in relation to the other phenothiazines now available for the treat-

ment of the conditions enumerated above, however, will have to await more carefully controlled studies. It is the feeling of this reviewer that the book has a useful place in the library of the busy practitioner as a bridge between the preclinical studies and the limited knowledge available. However, much could have been added to its stature by indicating some of the theoretical background which led to the introduction of this particular phenothiazine as an important new member of this group of drugs.

Albert A. Kurland

TAYLOR, JAMES, ED. *Selected Writings of John Hughlings Jackson (2 vols.)*. Basic Books, Inc., New York, 1958. xxii + 1010 pp. $15.00

There is no real need for a review (in the strict sense of the word) of this work. The only purpose of any remarks set forth here is to call to the attention of every student, neurologist and psychiatrist the fact that this remarkable classic is again available. For those who have never had the opportunity to read this work, the experience of doing so will be startling and long remembered; for those who previously have come into contact with this remarkable example of revolutionary thinking, knowledge, imagination, observation and clinical wisdom, the return to it will be unusually rewarding.

The editor has done an outstanding job of recreating the development of Hughlings Jackson's thought, from the early investigations of convulsive seizures (Volume I deals with epilepsy and epileptiform convulsions) and the famous research in the problems of epilepsy, chorea and hemiplegia, up to the later years in which his considerations extended into education, philosophy and other areas.

Jackson's writings extend through the period from 1861 to 1909. It has been pointed out before (and is more than obvious in the portion of his papers, contained in these two volumes) that his concepts of nervous system structure and function were far ahead of his time and, indeed, in many instances remain so even today. He was well aware, for example, of the necessity of taking into account certain genetic principles in any fundamental analysis of the operation of the nervous system. Nor was he unwilling to accept the concepts of psychology and psychiatry. The following quotation from a fascinating paper on "Words and other Symbols in Mentation" (published in 1893) serves as an example of the breadth of concept on which his thinking as a neurologist was based: "Words in themselves have no meaning; they are but symbols; ... words only come to have speech value when they are in propositions; to speak is to propositionise, it is not merely to utter words. ... Of course, a single word may be, in effect, a proposition, other words completing the proposition being understood, internally revived. Hence speaking is symbolising, a mental operation." He follows these remarks with considerations of ideation and perception which are radical and provocative. Nowhere is there any mental block on Jackson's part which might prevent him from finding the answers for which he sought.

One could continue at length to cite and analyze examples of his genius. Suffice it to say here, that these writings comprise one of the important documents of our cultural background and should become a part of the library and basic experience of everyone concerned with the nervous system and behavior.

Robert G. Grenell

ACKNOWLEDGMENTS

The Editorial and Advisory Board of JNMD represents a broad array of disciplines and specialties, but their collective sphere of competence does not match the enormous variety of subject matter in manuscripts that have been submitted. No editorial group of workable size could. We have solicited the assistance of the following people, who have served as consultants for manuscripts submitted during the past year. JNMD is dependent on the effort so generously contributed by these consultants, and their assistance is greatly appreciated.

Leo Abood
Harold Abramson
Marie Andersch
Russell Anderson
W. Ross Ashby
A. B. Baker
David L. Bazelon
Therese Benedek
Klaus Berblinger
Samuel Bessman
Bruno Bettelheim
Francis Board
Joseph V. Brady
Eugene B. Brody
Henry W. Brosin
Enoch Callaway, III
Mabel Cohen
Robert A. Cohen
Robert Cohn
Jules Coleman
Derek Denny-Brown
Oskar Diethelm
Leon Eisenberg
George Engel
Sibylle Escalona
L. Whiting Farinholt, Jr.
Stephen Fleck
Thomas M. French
Fritz A. Freyhan
Margaret Fries
W. Horsley Gantt
Norman Garmezy
Edwin Gildea
Bentley Glass
Mario Gazzano
William A. Greene, Jr.
Martin Gross
Heinz Hartmann
Arthur L. Haskins
Lewis B. Hill
Harold Himwich
Hudson Hoagland
Paul H. Hoch
Paul Hoefer
Ebbe C. Hoff
Edmund S. Howe
Stanley Imber
Walter O. Jahrreiss
Herbert H. Jasper
George A. Jervis
Lucie Jessner
Lothar Kalinowsky
Franz J. Kallman
Leo Kanner
Seymour Kety
Gerald D. Klee
Nathaniel Kleitman
Nathan S. Kline
Heinrich Klüver
Robert P. Knight
Othilda Krug
Lawrence S. Kubie
Albert A. Kurland
Leonard D. Kurland
Louis C. Lasagna
Stanley Lesse
Bertram D. Lewin
Howard Liddell
Theodore Lidz
John C. Lilley
Erich Lindemann
Reginald Lourie
Edith G. McGeer
Paul MacLean
Horace W. Magoun
Sidney Malitz
Henry Mark
Curtiss Marshall
Jack Mendelson
Moritz Michaelis
I. Arthur Mirsky
Roman Nagorka
John I. Nurnberger
Humphrey Osmond
Winfred Overholser
Gregory Pincus
Benjamin Pope
Florence Powdermaker
Dane G. Prugh
Jack Raher
David Rapaport
Fritz Redl
Frederick C. Redlich
Eli Robins
Philip Q. Roche
David Rosenthal
Milton S. Sacks
Seymour B. Sarason
Charles Savage
Leonard Scherlis
Nathan Shock
Arthur B. Silverstein
Harry C. Solomon
Rene Spitz
Alfred Stanton
Eliot Stellar
Mesrop Tarumianz
Oswei Temkin
Isadore Tuerk
Charles Van Buskirk
Jenny Waelder-Hall
Hans Weil-Malherbe
Walter Weintraub
Abraham Wikler
Lawson Wilkinson
Otto A. Will, Jr.
Abner Wolf
Harold G. Wolff
Herman Yannet
Imogene Young
Dewey K. Ziegler
Eugene Ziskind

INDEX, VOLUME 28

A

Abnormal behavior, early, 542
Abnormal mental conditions in infancy, 538
ACTH release and adrenocortical function and hypothalamic pathology, 332
Activation, subliminal, on, 293
Adams, Raymond D., 528
Adaptation and information in psychiatry, 204
Adrenergic stimulation, effect of on salivary component, 525
Adrenochrome and adrenolutin are psychotomimetic substances, 23
Adrenochrome model and schizophrenia, 18
Adrenocortical function, ACTH release and hypothalamic pathology, 332
Adrenopituitary activity, functional state of higher segments of central nervous system and, 438
Advanced psychiatric training
  and research must be organized separately, 120
  individualization of preferable to standardized curricula, 117
  subsidy of must replace inherited wealth, 118
Advanced training for psychiatric teaching and research, 115
Advances in psychiatry, social nature of, contributed by medically trained psychiatrists, 115
Afferent innervation of cortex, phylogenetic implications of (relation between nerve fiber size and sensory modality), 89
Afferent paths (cortical innervation), phylogenetic relations of, 98
Aggression, 378
Alcoholic hallucinosis, serum magnesium in delirium tremens and, 352
Allan, W. Scott, 371
Amine metabolism, 389
Amino acid uptake in brain, 390
Anesthetics and tranquilizers, narcotics and, 387
Aneurysms, ruptured, of anterior communicating artery, 309
Anoxia, effects on cortical dendritic spike, 8
Anxiety
  as a deterrent to pregnancy, 401
  function of magic thinking in, 402
Aphasia, semantic: II, 302
  site of lesion in, 302
  type of disorder, 302
Aprison, M. H., 249
Arfonad (trimethaphan) hypotension, effects on cortical dendritic spike, 7
Arteriosclerotic psychoses, 160
Artery, anterior communicating, ruptured aneurysms of, 309
Associative processes, effect of LSD on, 409
Attitudes, investigators' and therapists', effects of in evaluation of tranquilizers prescribed to hospital patients, 256
Austin, D. C., 249
Autism, early infantile, a re-evaluation, 539
Autonomic changes in schizophrenia and model psychoses, 27
Autonomic drugs, effect of on salivary component, 523
Autonomic stimulation, response of a tyramine-like component of human saliva to, 520

B

Banshchikov, V. M., 160
Barron, Kevin D., 497
Bates, Richard, 12
Batkin, Stanley, 558
Bauer, Hans G., 323
Behavior to objects and to persons, differences in, primitive reaction types and, 544
Behavioral response to convulsive therapy, psychological factors affecting individual differences in, 243
Benadryl, effects on cortical dendritic spike, 5
Berg, Morton, 365
Berg, Seymour, 239
Bias, elimination of in design of experiments on psychological effects of drugs, 129
Bibliography of Parapsychology, 566
Biochemistry
  adrenochrome model and schizophrenia, 18
  Hopkins-Cole reaction in schizophrenic urine, observations on, 456
  tryptophan content of urines of schizophrenics and other psychotic patients, 459
Bishop, George H., 89
Bleeding tendency, massive retroperitoneal hemorrhage in patient with: unusual complication of electroshock therapy, 187
Blood brain barrier, 385
Blood protein disturbances and hypothalamus, 335
Blum, Lucille Hollander, 401
Blumenthal, Irving J., 562
Body as object, the (note on theory of homosexuality, 179
Body image, right-left body reactivity patterns in disorganized states, 396
Brain
  blood brain barrier, 385
  glucose metabolism in, 382
  gross examination of, of second known case of semantic aphasia, 304
  metabolism and function, substrates of, 384
  oxygen and the, 381

Brain Memory Learning, 467
Brengelmann, J. C., 469
Broadbent, D. E., 378
Brodal, Alf, 463
Brody, Eugene B., 182
Brummit, Houston, 187

C

Callowhill, C. R., 453
Cameron, John L., 465
Capacity, development of in personality, 208
Carbon dioxide, effects on cortical dendritic spike, 6
Care of the Geriatric Patient, The, 462
Categorization width of Korsakoff patients, 215
Cationic effects in neurochemistry, 387
Central nervous system
  functional state of higher segments of, and adrenopituitary activity, 438
  mammalian, general physiology and pharmacology of synapses and, 473
Cerebral dysfunction, presumed measure of (effect of electroconvulsive treatment on perception of spiral aftereffect), 239
Cerebrospinal fluid, 86
  neuraminic acid in Parkinsonism and schizophrenia, 450
Ceruloplasmin (serum oxidase) inhibition by tryptophan metabolites, studies on, 249
Chemotherapy
  agents acting on cortical dendritic spike, pharmacological selectivity by, 1
  chlorpromazine and secobarbital, effects of on C.P.T., 12
  chlorpromazine, effects of on psychomotor, psychiatric behavior of chronic schizophrenics, 358
  drugs, psychological effects of, design and conduct of experiments on, 129
  meprobamate, effect of on stuttering, 558
  N,N-dimethyl-p-phenylene-diamine hydrochloride (DPP), relationship of to mental health, 453
Chisholm, Brock, 370
Chlorpromazine
  effects of on psychomotor, psychiatric behavior of chronic schizophrenics, 358
  and secobarbital, effects of on C.P.T., 12
  effects on cortical dendritic spike, 4
Chertok, L., 227
Choline, syntheses involving, 386
Cholinergic stimulation, effect of on salivary component, 524
Chronic Schizophrenia, 465
Civil and criminal cases, epilepsy in, 272
Classification of objects by Korsakoff patients, 218
Cleveland, Sidney E., 396
Clinical
  EEG interpretation, reliability of, 425
  etio-pathogenetic, therapeutic, and neuropathologic considerations in multiple sclerosis, 279, 282
Cohen, Bernard B., 365
Comparison of effects of investigators' and therapists' attitudes in evaluation of tranquilizers prescribed to hospital patients, 256
Concentrations of drugs, control of in psychological experiments on effects of drugs, 141
Concept formation in Korsakoff's psychosis, 214
  sequential, 221
Concept of split social field as a determinant of schizophrenic excitement, 182
Conduct and design of experiments on psychological effects of drugs, 129
Confounding of psychological effects of drugs in experiments, 138
Contact with persons, 546
Contributions of enzymology to neurochemistry, 381
Convulsive disorders, emotional activation of the encephalogram in patients with, 339
Cortex
  mammalian, stages in evolution of, 106
  phylogenetic implications of afferent innervation of (relation between nerve fiber size and sensory modality), 89
Cortical dendritic spike and its slow aftereffects, pharmacological selectivity by agents acting on, 1
Cortical dendritic spike, effects on of,
  anoxia, 8
  Arfonad (trimethaphan) hypotension, 7
  Benadryl, 5
  carbon dioxide, 6
  chlorpromazine, 4
  ether, 6
  hypotension by exsanguination, 7
  nembutal, 3
  nitrous oxide, 6
  procaine, 4
Costello, R. T., 463
C.P.T. (Continuous Performance Test), effects of chlorpromazine and secobarbital on, 12
Cowdry, E. Vincent, 462
Crandall, Archie, 148
Criminal and civil cases, epilepsy in, 272
Critical attributes of objects, discovery of by Korsakoff patients, 219
Crosley, Archer P., Jr., 125
Convulsive therapy, psychological factors affecting individual differences in behavioral response to, 243
Cybernetics and certain modern problems of nervous system physiology, 169

D

Delirium tremens and alcoholic hallucinosis, serum magnesium in, 352
Dendritic spike, cortical, and its slow after-effects, pharmacological selectivity by agents acting on, 1
Design and conduct of experiments on psychological effects of drugs, 129
  elimination of bias in, 129
  essential versus economic considerations, 133
  reduction of experimental error in, 129
  subject selection, 130
Development of capacity in personality, 208
Diagnosis of epilepsy, value of photic stimulation in, 508
DiCarlo, L. M., 558
Differences in behavior to objects and to persons, primitive reaction types and, 544
Discovery of critical attributes of objects by Korsakoff patients, 219
Disorder, type of, in semantic aphasia, 302
DPP (N,N-dimethyl-p-phenylene-diamine hydrochloride), relationship of mental health to oxidation of, 453
Driving and epilepsy, 268
Drug- and play-therapy, effect of on fecal incontinence in chronic schizophrenics, 562
Drugs
  autonomic, effect of on salivary component, 523
  psychological effects of, design and conduct of experiments on, 129
Dysthermia, hypogonadism and hypothalamus, 331

E

Early abnormal behavior, 542
Early infantile autism: re-evaluation, 539
Early separation from the mother in schizophrenia, 365
Edelstein, E. L., 459
Edwards, Allen L., 371
EEG
  epilepsy, diagnosis of, value of photic stimulation in, 508
  reliability of clinical interpretation of, 425
Effect of electroconvulsive treatment on perception of spiral aftereffect, a presumed measure of cerebral dysfunction, 239
Effect of LSD on the associative processes, 409
Effect of meprobamate on stuttering, exploratory investigation of, 558
Effect of various therapies on fecal incontinence in chronic schizophrenics, 562
Effects of chlorpromazine and secobarbital on C.P.T., 12
Effects of chlorpromazine on psychomotor and psychiatric behavior of chronic schizophrenics, 358
Effects of investigators' and therapists' attitudes in evaluation of tranquilizers prescribed to hospital patients, 256
Effects, psychological, of drugs, design and conduct of experiments on, 129
Ego strength and length of recovery from infectious mononucleosis, 125
Eisen, Sydney B., 256
Electroconvulsive therapy, psychological factors affecting individual differences in behavioral response to, 243
Electroconvulsive treatment, effect of on perception of spiral aftereffect, a presumed measure of cerebral dysfunction, 239
Electroencephalogram
  emotional activation of in patients with convulsive disorders, 339
  and epilepsy, 265
Electro-encephalography, hypnosis, sleep and, 227
Electrophysiological properties of synapses, 474
Electrophysiology
  and pharmacology, compared, of synapses, 490
  cortical dendritic spike, pharmacological selectivity by agents acting on, 1
Electroshock therapy, unusual complication of: massive retroperitoneal hemorrhage in patients with bleeding tendency, 187
Ellingson, Robert J., 425
Emotional activation of the electroencephalogram in patients with convulsive disorders, 339
Endocrine and metabolic conditions related to pathology in hypothalamus: A review, 323
Engelhardt, David M., 562
Enzymology, contributions of to neurochemistry, 381
Epilepsy
  and driving, 268
  and the electroencephalogram, 265
  and the law, 262
  convulsive disorders, emotional activation of EEG in patients with, 339
  definition of, 262
  heredity and marriage and, 266
  in criminal and civil cases, 272
  incidence and course of, 264
  types of, 263
  value of photic stimulation in diagnosis of, 508
  work, workmen's compensation and, 271
Essential versus economic considerations in design of experiments on psychological effects of drugs, 133
Estimation-research vs. hypothesis-testing, 195
Ether, effects of on cortical dendritic spike, 6
Etio-pathogenetic, neuropathologic, clinical and therapeutic considerations in multiple sclerosis, 279, 284
Evaluation of tranquilizers prescribed to hos-

pital patients, effects of investigators' and therapists' attitudes in, 256
Evolution
of human neurotic process, universals in, 72
of excitable membranes, 473
of mammalian cortex, stages in, 106
Experiments on psychological effects of drugs
design and conduct of, 129
reduction of experimental error in design of, 129
Exploratory investigation of the effect of meprobamate on stuttering behavior, 558
Eysenck, H. J., 469

F

Fecal incontinence in chronic schizophrenics, effect of various therapies on, 562
Femininity, acknowledgment of and pregnancy, 405
Ferraro, Armando, 279
Fine, David I. M., 497
Fink, Max, 243
Fisher, Seymour, 396
Fluorophore, salivary, detection and characterization of, 520
Freedman, Norbert, 562
Freeman, Thomas, 465
Full-time man concept in psychiatry, 119
Function and metabolism of brain, substrates of, 384
Functional state of higher segments of central nervous system and adrenopituitary activity, 438

G

General intellectual functions in Korsakoff's psychosis, 528
General physiology and pharmacology of synapses and some implications for mammalian central nervous system, 473
Glanz, E. C., 568
Glucose metabolism in the brain, 382
Glyoxylic acid reaction
in urine of schizophrenics, 456
positive, in urine of mental patients, 184
Goldring, Sidney, 1
Goldstein, Kurt, 538
Granger, G. W., 469
Greenfield, Norman S., 125
Greystone (N. J. State Hospital) population, survey of, 153
Grundfest, Harry, 473
GSR, right-left body reactivity patterns in disorganized states, 396
Gurevich, B. Kh., 169

H

Hallucinosis, alcoholic, serum magnesium in delirium tremens and, 352
Hankoff, Leon D., 562
Hanson, K. M., 249
Heath, Helen, 256
Heilizer, Fred, 358
Hellinger, Bernard S., 456
Hemorrhage, massive retroperitoneal, in patient with bleeding tendency; unusual complication of electroshock therapy, 187
Heredity, epilepsy, and marriage, 266
Hess, Walter C., 450
Higher segments of central nervous system, functional state of, and adrenopituitary activity, 438
Hildebrand, J. H., 468
Hirano, Asao, 309
Hoffer, A., 18
Hopkins-Cole reaction in urine of schizophrenics, observations on, 456
Hospital patients, effects of investigators' and therapists' attitudes in evaluation of tranquilizers prescribed, 256
Houfek, Edward E., 425
Huang, Shi H., 1
Human neurotic process, universals in evolution of, 72
Human saliva, studies on: Tyramine-like component and autonomic stimulation, 520
Hypnosis, sleep and electro-encephalography, 227
Hypogonadism
and hypothalamic pathology, 330
associated with dysthermia, and hypothalamus, 331
Hypotension by exsanguination, effects on cortical dendritic spike, 7
Hypothalamic
dysfunction and obesity, 331
pathology, ACTH release and adrenocortical function and, 332
pathology, water metabolism as affected by, 327
Hypothalamus
and blood protein disturbances, 335
and hypogonadism, 330
and precocious puberty, 330
pathology in, endocrine and metabolic conditions related to (review), 323
sexual development and function as influenced by, 329
thyroid stimulating hormone and thyroid function and, 335
Hypothesis-testing vs. estimation-research, 195

I

Iker, Howard P., 191
Incidence of neurologic disorders in psychiatric institutions, available data on, 149
Incontinence, fecal, in chronic schizophrenics, effect of various therapies on, 562
Individual differences in behavioral response to

convulsive therapy, psychological factors affecting, 243
Individualization of advanced psychiatric training preferable to standardized curricula, 117
Infancy, abnormal mental conditions in, 538
Infantile autism, early, a re-evaluation, 539
Infectious mononucleosis, ego strength and length of recovery from, 125
Information and adaptation in psychiatry, 204
Inhibition by tryptophan metabolites of serum oxidase (ceruloplasmin), studies on, 249
Innervation, afferent, of cortex, phylogenetic implications of (relation between nerve fiber size and sensory modality), 89
Intellectual functions, general, in Korsakoff's psychosis, 528
Interpretation, clinical, of EEG, reliability of, 425
Introduction to Personal Adjustment, An, 568
Investigations on tryptophan content of urines of schizophrenics and other psychotic patients, 459
Investigators' and therapists' attitudes, effects of in evaluation of tranquilizers prescribed to hospital patients, 256

J

Jackson, John Hughlings, Selected Writings, 573
Jasper, H. H., 463

K

Kahn, Robert L., 243
Katz, Jack, 558
Klee, Gerald D., 409
Klein, George S., 293
Knighton, R. S., 463
Korsakoff's psychosis, psychological studies of: I. General intellectual functions, 528
Korsakoff's psychosis, psychological studies of: III. Concept formation, 214
categorization width, 215
classification, 218
critical attributes, 219
sequential concept formation, 221
Kramarz, P., 227
Krassilowsky, D., 459
Kubie, Lawrence S., 65, 81
Kubzansky, Philip, 352

L

Law, the, and epilepsy, 262
Learning, in experiments on psychological effects of drugs, 139
Leiderman, P. Herbert, 352
Lesion, site of in semantic aphasia, 302
Leventhal, Fred, 187
Liebman, Samuel, 467
Liver function changes in schizophrenia and model psychoses, 27
Lives in Progress: A Study of the Natural Growth of Personality, 566
LSD,
effect of on associative processes, 409
right-left body reactivity patterns under as compared to schizophrenics, 396
Lukianowicz, N., 36

M

Magic power of the maternal figure, sterility and, 401
Magic thinking in anxiety, function of, 402
Magnesium, serum, in delirium tremens and alcoholic hallucinosis, 352
Mammalian central nervous system, general physiology and pharmocolgy of synapses and, 473
Mammalian cortex, stages in evolution of, 106
Marriage, epilepsy, heredity, and, 266
Massive retroperitoneal hemorrhage in patient with bleeding tendency: unusual complication of electroshock therapy, 187
Maternal figure
perceived as malevolent, 404
sterility and the magic power of, 401
McGhie, Andrew, 465
McLane, John E., 450
Measure of cerebral dysfunction, presumed (effect of electroconvulsive treatment on perception of spiral aftereffect), 239
Medically trained psychiatrists, social nature of advances in psychiatry contributed by, 115
Melsen, S., 508
Mendelson, Jack, 352
Menninger, Karl, 571
Mental conditions, abnormal, in infancy, 538
Mental health, relationship to oxidation of N,N-dimethyl-p-phenylene-diamine hydrochloride (DPP), 453
Mental patients, positive glyoxylic acid reaction in urine of, 184
Membranes, excitable, evolution of, 473
Meprobamate, effect of on stuttering, exploratory investigation of, 558
Metabolic and endocrine conditions related to pathology in hypothalamus: A review, 323
Metabolism and function of brain, substrates of, 384
Metabolism
glucose, in the brain, 382
of amines, 389
of water as affected by hypothalamic pathology, 327
Metabolites, tryptophan, studies on serum oxidase (ceruloplasmin) inhibition by, 249
Metcalf, John S., 1
Mettler, Fred A., 148
Mirsky, Allan F., 12

Model, adrenochrome, and schizophrenia, 18
Model psychoses
autonomic changes in schizophrenia and, 27
liver function changes in schizophrenia and, 27
urinary constituents, changes in schizophrenia and, 27
Mononucleosis, infectious, ego strength and length of recovery from, 125
Mother, early separation from in schizophrenia, 365
Multiple sclerosis
clinical considerations, 282
etio-pathogenetic considerations, 284
neuropathologic, clinical, etio-pathogenetic and therapeutic considerations in, 279
neuropathologic considerations, 280
therapeutic considerations, 287

N

Narcotics, anesthetics and tranquilizers, 387
Nash, Harvey, 129
Nature of the neurotic process, 66
Nembutal, effects on cortical dendritic spike, 3
Neocortex, sizes of nerve fibers innervating, 103
Nerve fiber size and sensory modality, relation between: Phylogenetic implications of afferent innervation of cortex, 89
Nerve fibers innervating neocortex, sizes of, 103
Nervous system, central
functional state of higher segments of, and adrenopituitary activity, 438
(mammalian), general physiology and pharmacology of synapses and, 473
Nervous system, cybernetics and certain modern problems of physiology of, 169
Neuraminic acid in cerebrospinal fluid, in Parkinsonism and schizophrenia, 450
Neurochemistry, contributions of enzymology to, 381
Neurologic and psychiatric disorders, nature of relationship between, 151
Neurologic disorders in psychiatric institutions, 148
available data on incidence of, 149
difficulties with existing statistics on, 148
Neuromyositis, 497
Neuropathologic, clinical, etiopathogenetic and therapeutic considerations in multiple sclerosis, 279, 280
Neurotic Distortion of the Creative Process, 81
Neurotic process
nature of, 66
roots, trunk and branches of, 70
social forces and, 65
universals in evolution of, 72
Nitrous oxide, effects on cortical dendritic spike, 6
N,N-dimethyl-p-phenylene-diamine hydrochloride (DPP) relationship of mental health to oxidation of, 453
Noshay, W. C., 463
Note on concept of split social field as a determinant of schizophrenic excitement, 182
Note on the theory of homosexuality: the body as object, 179

O

Obesity and hypothalamic dysfunction, 331
Object, the body as (note on theory of homosexuality), 179
Objects and persons, differences in behavior to, primitive reaction types and, 544
Observations on the Hopkins-Cole reaction in urine of schizophrenics, 456
O'Connor, Cecilia M., 86
O'Doherty, Desmond, 450
O'Leary, James L., 1
On the reliability of clinical EEG interpretation, 425
Organization of a division for postgraduate psychiatric training and research, 121
Osmond, H., 18
Oxidation of N,N-dimethyl-p-phenylene-diamine hydrochloride (DPP), relationship of to mental health, 453
Oxley, Beatrice, 239
Oxygen and the brain, 381

P

Pachter, M. Richard, 456
Papadopoulos, Nicholas M., 450
Parasagittal syndrome produced by trauma, 276
Parkinsonism and schizophrenia, cerebrospinal fluid neuraminic acid in, 450
Patterns of right-left body reactivity in disorganized states, 396
Perception and Communication, 378
Perception of spiral aftereffect, effect of electroconvulsive treatment on, a presumed measure of cerebral dysfunction, 239
Perceptual Processes and Mental Illness, 469
Perr, Irwin N., 262
Persons and objects, differences in behavior to, primitive reaction types and, 544
Persons, contact with, 546
Pharmacological considerations in psychological effects of drugs, experiments on, 140
Pharmacological properties of synapses, 482
Pharmacological selectivity manifested by agents acting upon the cortical dendritic spike and its slow after-effects, 1
Pharmacology and electrophysiology, compared, of synapses, 490
Pharmacology and physiology, general, of synapses and some implications for mammalian central nervous system, 473

Philippopoulos, G. S., 415
Photic stimulation, value of in diagnosis of epilepsy, 508
Phylogenetic implications of afferent innervation of cortex (relation between nerve fiber size and sensory modality), 89
Phylogenetic relations of afferent paths (cortical innervation), 98
Physiological analysis of sensory paths (afferent innervation of cortex), 96
Physiology and pharmacology, general, of synapses and some implications for mammalian central nervous system, 473
Physiology of the nervous system, cybernetics and certain modern problems of, 169
Physiopathology of thyrotoxicosis, 416
Play- and drug-therapy, effect of on fecal incontinence in chronic schizophrenics, 562
Pollack, Max, 243
Polysaccharides in Biology, 373
Population characteristics in sampling, 196
Positive glyoxylic acid reaction in urine of mental patients, 184
Postgraduate psychiatric training and research, organization of a division for, 121
Practical and theoretical aspects of sampling procedures in research, 191
Pregnancy
  acknowledgment of femininity and, 405
  anxiety as a deterrent to, 401
  case of, after decision to adopt, 401
Prescription for Survival, 370
Primac, Daniel W., 12
Primitive reaction types and differences in behavior to objects and to persons, 544
Procaine, effects of on cortical dendritic spike, 4
Proceedings of Four Conferences of Parapsychological Studies, 566
Proctor, L. D., 463
Projection levels, primary, of sensory paths (cortical), 102
Pseudo-social behavior, 548
Psychiatric and neurologic disorders, nature of relationship between, 151
Psychiatric and psychomotor behavior of chronic schizophrenics, effects of chlorpromazine on, 358
Psychiatric institutions
  as principal source of clinical research material, 148
  available data on incidence of neurologic disorders in, 149
  difficulties with existing statistics on neurologic conditions in, 148
  neurologic disorders in, 148
Psychiatric teaching and research, advanced training for, 115
Psychiatric training, advanced
  and research must be organized separately, 120
  and research, organization of a division for, 121
  full-time man concept left over from feudal times, 119
  individualization of preferable to standardized curricula, 117
  must strengthen the psychiatrist to manage conflicts and withstand scientific doubts, 116
  subsidy of must replace inherited wealth, 118
Psychiatric training and research, postgraduate, need for separate division for, 121
Psychiatrists, medically trained, social nature of advances in psychiatry contributed by, 115
Psychiatry
  adaptation and information in, 204
  advances in have been contributed by medically trained psychiatrists, 115
Psychoanalytical theory of transvestism, 41
Psychodynamics and psychosomatic observations in thyrotoxicosis, 417
Psychological conditioning theory of transvestism, 39
Psychological effects of drugs
  confounding of in experiments on, 138
  control of effective concentrations in experiments on, 141
  importance of suggestion in experiments on, 136
  learning in experiments on, 139
  pharmacological considerations in experiments on, 140
  psychological considerations affecting experimental outcomes, 136
  secondary drug effects in experiments on, 140
  short-term versus long-term effects in experiments on, 141
Psychological factors affecting individual differences in behavioral response to convulsive therapy, 243
Psychological studies of Korsakoff's psychosis
  I. General intellectual functions, 528
  III. Concept formation, 214
Psychomotor and psychiatric behavior of chronic schizophrenics, effects of chlorpromazine on, 358
Psychopathology, psychodynamics, and psychosomatic observations in thyrotoxicosis, 417
Psychoses
  arteriosclerotic, 160
  symbiotic, re-evaluation of, 550
Psychosis, Korsakoff's, psychological studies of
  I. General intellectual functions, 528
  III. Concept formation, 214
Psychosis, symbiotic, symptomatology of, 553
Psychosomatic approach to thyrotoxicosis, 415
Psychosomatic observations, psychopathology and psychodynamics in thyrotoxicosis, 417

Psychotic patients, schizophrenics and other, tryptophan content of urines of, 459
Psychotomimétic antagonists and schizophrenic therapeutic agents, 26
Puberty, precocious, with hypothalamic lesions, 330

Q

Quastel, J. H., 381

R

Reaction types, primitive, and differences in behavior to objects and to persons, 544
Recovery from infectious mononucleosis, length of, and ego strength, 125
Re-evaluation of early infantile autism, 539
Re-evaluation of symbiotic psychoses, 550
Rehabilitation: A Community Challenge, 371
Relation between nerve fiber size and sensory modality: Phylogenetic implications of afferent innervation of cortex, 89
Relation of Psychiatry to Pharmacology, The, 567
Relationship of mental health to oxidation of N,N-dimethyl-p-phenylene-diamine hydrochloride (DPP), 453
Reliability of clinical EEG interpretation, 425
Research and advanced psychiatric training must be organized separately, 120
Research and teaching, psychiatric, advanced training for, 115
need for separate division, 121
Research, sampling procedures in, some theoretical and practical aspects of, 191
Response, behavioral, to convulsive therapy, psychological factors affecting individual differences in, 243
Reticular Formation of the Brain, 463
Reticular Formation of the Brain Stem, The 463
Retroperitoneal hemorrhage, massive, in patient with bleeding tendency: unusual complication of electroshock therapy, 187
Riese, Walther, 302
Rifkin, Alfred, 239
Right-left body reactivity patterns in disorganized states, 396
Robbins, Edwin S., 239
Roessler, Robert, 125
Roots, trunk and branches of the neurotic process, 70
Ruesch, Jurgen, 115
Ruptured aneurysms of anterior communicating artery, 309
Russell, W. Ritchie, 467

S

Sabshin, Melvin, 256
Sakel, Manfred, 373
Saliva, human, studies on: Tyramine-like component and autonomic stimulation, 520
Salivary fluorophore, detection and characterization of, 520
Samples, size of, 199
Sampling procedures in research, some theoretical and practical aspects of, 191
Schenker, Anne C., 520
Schenker, Victor, 520
Schizophrenia, 373
adrenochrome model and, 18
autonomic changes in model psychoses and, 27
cerebrospinal fluid neuraminic acid in Parkinsonism and, 450
early separation from the mother in, 364
liver function changes in model psychoses and, 27
right-left body reactivity patterns in, 396
similarity of experimental psychoses and, 25
urinary constituents, changes in model psychoses and, 27
Schizophrenic and non-schizophrenic fluids, biochemical differentiation of, 19
Schizophrenic excitement, split social field as a determinant of, concept of, 182
Schizophrenics
chronic, effect of various therapies on fecal incontinence in, 562
chronic, effects of chlorpromazine on psychomotor, psychiatric behavior of, 358
observations on Hopkins-Cole reaction in urine of, 456
tryptophan content of urines of, and other psychotic patients, 459
Science in the Making, 468
Scientific and Technical Translating and Other Aspects of the Language Problem (UNESCO Report), 85
Scott, John Paul, 378
Secobarbital and chlorpromazine, effects of on C.P.T., 12
Secondary drug effects, design of psychological drug experiments and, 140
Seidenberg, Robert, 179
Selected Writings of John Hughlings Jackson, 573
Semantic aphasia: II, 302
report of second known case of, 303
Sensory modality and nerve fiber size, relation between: Phylogenetic implications of afferent innervation of cortex, 89
Sensory paths
physiological analysis of, 96
primary projection levels of (cortical), 102
Separation, early, from the mother in schizophrenia, 365
Sequential concept formation in Korsakoff patients, 221

Serum magnesium in delirium tremens and alcoholic hallucinosis, 352
Serum oxidase (ceruloplasmin) inhibition by tryptophan metabolites, studies on, 249
Sexual development and function as influenced by hypothalamus, 329
Shands, Harley C., 204
Shields, John, 1
Short-term versus long-term effects of drugs, in design of experiments on psychological effects of, 141
Silverstein, Arthur B., 409
Site of lesion in semantic aphasia, 302
Size of samples, 199
Sizes of nerve fibers innervating neocortex, 103
Sleep, hypnosis and electro-encephalography, 227
Smith, Kline and French Laboratories Staff, 572
Social Desirability Variable in Personality Assessment and Research, The, 371
Social forces and the neurotic process, 65
Social nature of advances in psychiatry, contributed by medically trained psychiatrists, 115
Solomon, Philip, 352
Some theoretical and practical aspects of sampling procedures in research, 191
Spiral aftereffect, effect of electroconvulsive treatment on perception of, a presumed measure of cerebral dysfunction, 239
Split social field as a determinant of schizophrenic excitement, concept of, 182
Springer, Georg F., 373
Stages in evolution of mammalian cortex, 106
Statistics, existing, on neurologic conditions in psychiatric institutions, difficulties with, 148
Stennett, R. G., 453
Sterility and the magic power of the maternal figure (a case of pregnancy after decision to adopt), 401
Stevens, Janice R., 339
Stimulation
  adrenergic, effect of on salivary component, 525
  autonomic, response of a tyramine-like component of human saliva to, 520
  cholinergic, effect of on salivary component, 524
  photic, value of in diagnosis of epilepsy, 508
Stoliarov, G. V., 160
Studies on human saliva: Tyramine-like component and its response to autonomic stimulation, 520
Studies on serum oxidase (ceruloplasmin) inhibition by tryptophan metabolites, 249
Stuttering, effect of meprobamate on, exploratory investigation of, 558
Subliminal activation, on, 293
Subject selection in design of experiments on psychological effects of drugs, 130
Subsidy of advanced psychiatric training must replace inherited wealth, 118
Substrates of brain metabolism and function, 384
Suggestion, as affects results of experiments on psychological effects of drugs, 136
Survey of various aspects of transvestism in the light of our present knowledge, 36
Symbiotic psychoses
  re-evaluation of, 550
  symptomatology of, 553
Synapses, general physiology and pharmacology of and some implications for mammalian central nervous system, 473
Syntheses involving choline, 386

T

Talland, George A., 214, 528
Taylor, James, 573
Teaching and research, psychiatric, advanced training for, 115
Techniques of sampling in research, 192
Terry, Robert D., 309
Thalamocortical interaction, 109
Theoretical and practical aspects of sampling procedures in research, 191
Theory of homosexuality, note on: the body as object, 179
Theory of Psychoanalytic Technique, 571
Therapeutic considerations in multiple sclerosis, 279, 287
Therapists' and investigators' attitudes, effects of in evaluation of tranquilizers prescribed to hospital patients, 256
Therapy, play- and drug-, effect of on fecal incontinence in chronic schizophrenics, 562
Thyrotoxicosis
  and its psychosomatic approach, 415
  physiopathology of, 416
  psychosomatic observations, psychopathology and psychodynamics of, 417
Trachik, V., 438
Training, advanced, for psychiatric teaching and research, 115
Tranquilizers, narcotics, anesthetics and, 387
Tranquilizers prescribed to hospital patients, effects of investigators' and therapists' attitudes in evaluation of, 256
Transport phenomena in neurochemistry, 391
Transsexualism and transvestism, 49
Transvestism
  age of onset, 51
  and heredity, 54
  and other sexual deviations, 47
  and psychoneurosis, 54
  and the law, 56
  and transsexualism, 49
  classifications of, 37

clinical picture of, 43
definitions of, 37
etiology of, 38
female, question of, 43
frequency of occurrence of, 52
multifactorial theories of, 42
non-sexual explanations of, 43
progress and outcome of, 52
psychoanalytical theory of, 41
psychological conditioning theory of, 39
role of cultural factors in, 55
role of in marriage, 55
sex distribution in, 53
sexual drive in, 45
survey of various aspects of in the light of our present knowledge, 36
symptomatology of, 43
terminology, 36
theories of organic origin of, 38
theory of divine origin of, 38
theory of psychological conditioning in, 39
treatment of, 58
Trauma, parasagittal syndrome produced by, 276
Trifluoperazine: Clinical and Pharmacological Aspects, 572
Tryptophan content of urines of schizophrenics and other psychotic patients, 459
Tryptophan metabolites, studies on serum oxidase (ceruloplasmin) inhibition by, 249
Type of disorder in semantic aphasia, 302
Tyramine-like component of human saliva and autonomic stimulation, 520
effect of adrenergic stimulation on, 525
effect of autonomic drugs on, 523
effect of cholinergic stimulation on, 524

U

Understanding Your Patient, 467
Universals in evolution of human neurotic process, 72
Unusual complication of electroshock therapy: massive retroperitoneal hemorrhage in patient with bleeding tendency, 187
Urinary constituents, changes in, in schizophrenia and model psychoses, 27
Urine
of mental patients, positive glyoxylic acid reaction in, 184
of schizophrenics, observations on Hopkins-Cole reaction in, 456
of schizophrenics and other psychotic patients, tryptophan content of, 459

V

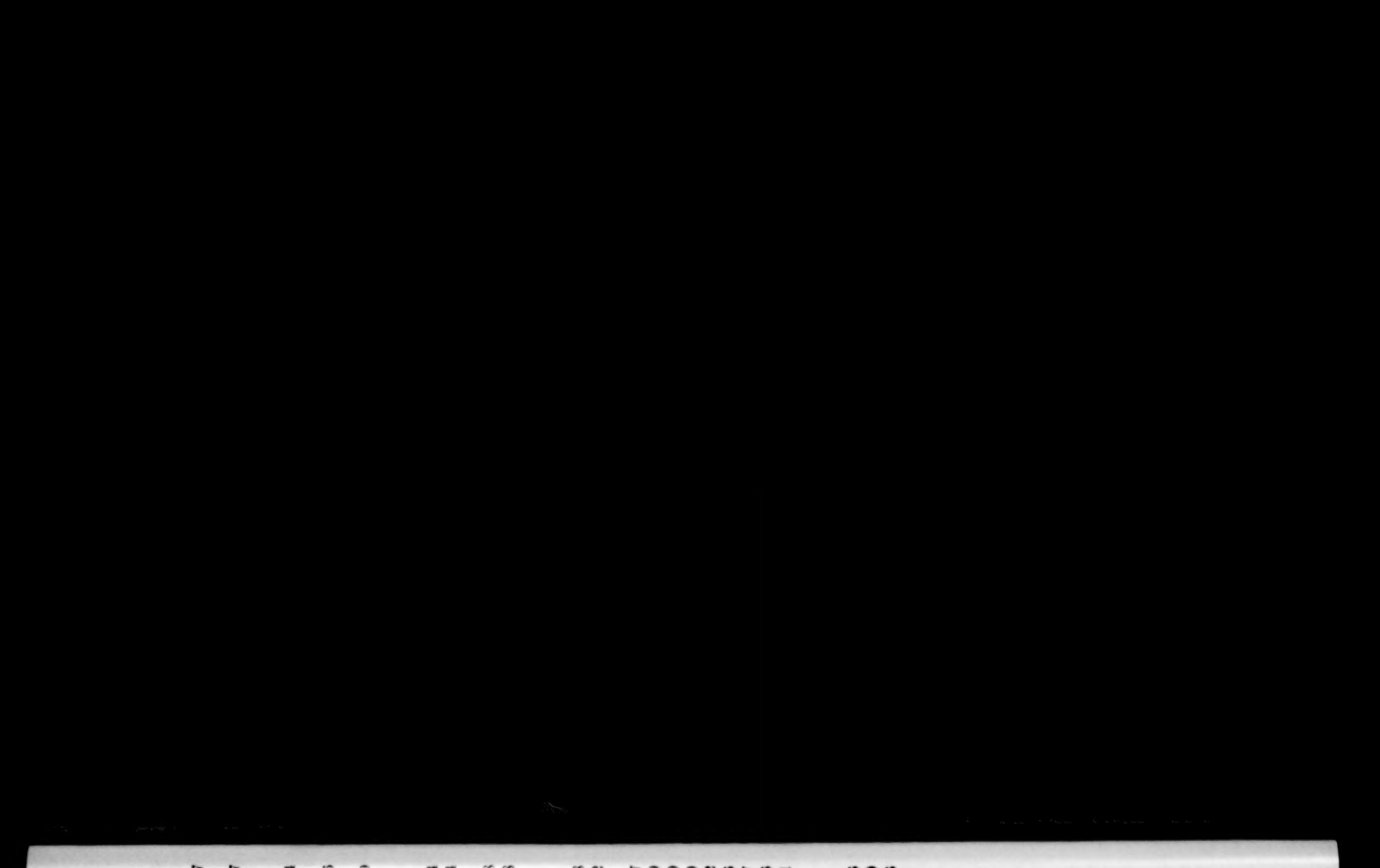
Valentova, M., 184
Velek, M., 184
Value of photic stimulation in diagnosis of epilepsy, 508
Victor, Maurice, 528

W

Walston, E. B., 568
Warshaw, Leon, 562
Water metabolism as affected by hypothalamic pathology, 327
Wechsler, David, 239
Weinstein, Sidney, 239
Weintraub, Walter, 409
Wexler, Donald, 352
White, Robert W., 566
Wikler, Abraham, 567
Wolstenholme, G. E. W., 86
Workmen's compensation, epilepsy, work, and, 271

Z

Ziegler, Dewey K., 276
Zimmerman, H. M., 309
Zorab, George, 566



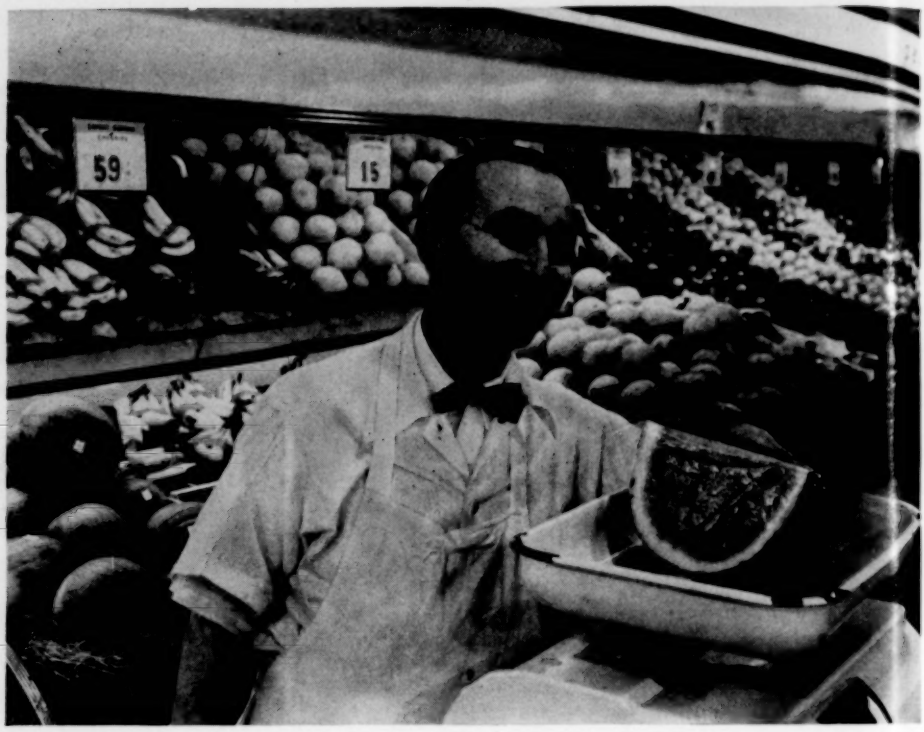
57
57
4
6
9
4
4
8
8
8
2
7
9
9
9
2
6
5
3
1
3

Volume 128 · Number 6 · June 1959

DOES NOT CIRCULATE

THE UNIVERSITY OF MICHIGAN
AUG 7 1959
MEDICAL LIBRARY

Published monthly by
THE WILLIAMS & WILKINS COMPANY



the epileptic... 1959

The happiness of work, of laughter, of *belonging*—priceless possessions, these, for the epileptic patient. Yet, how recently were these freedoms won! Today, his future is more hopeful than ever before, thanks in part to a finer and growing knowledge of the disease—and the more effective antiepileptic drugs. Presented here are five distinguished anticonvulsants that will help you give your patients that most precious of all gifts: a normal life.

PEGANONE®
(Ethotoin, Abbott)

A hydantoin of exceptionally low toxicity for *grand mal* and psychomotor seizures.

PHENURONE®
(Phenacemide, Abbott)

Often effective where other therapy fails in *grand mal, petit mal,* psychomotor and mixed seizures.

GEMONIL®
(MetharbItal, Abbott)

Relatively non-toxic, for *grand mal, petit mal,* myoclonic and mixed seizures symptomatic of organic brain damage.

TRIDIONE®
(Trimethadione, Abbott)

PARADIONE®
(Paramethadione, Abbott)

Homologous agents for symptomatic control of *petit mal,* myoclonic and akinetic seizures.

902058

ANTICONVULSANTS BY ABBOTT

Published monthly by The Williams & Wilkins Co., 428 E. Preston St., Baltimore 2, Md., U. S. A.
Subscription price $15.00, single issue $1.50
Second-class postage paid at Baltimore, Md.

Table of Contents

GENERAL PHYSIOLOGY AND PHARMACOLOGY OF SYNAPSES AND SOME IMPLICATIONS FOR THE MAMMALIAN CENTRAL NERVOUS SYSTEM. *Harry Grundfest* 473

NEUROMYOSITIS. *Kevin D. Barron and David I. M. Fine* 497

THE VALUE OF PHOTIC STIMULATION IN THE DIAGNOSIS OF EPILEPSY. *S. Melsen* 508

STUDIES ON HUMAN SALIVA: A TYRAMINE-LIKE COMPONENT AND ITS RESPONSE TO AUTONOMIC STIMULATION. *Victor Schenker and Anne C. Schenker* 520

PSYCHOLOGICAL STUDIES OF KORSAKOFF'S PSYCHOSIS: I. GENERAL INTELLECTUAL FUNCTIONS. *Maurice Victor, George A. Talland and Raymond D. Adams* 528

ABNORMAL MENTAL CONDITIONS IN INFANCY. *Kurt Goldstein* 538

AN EXPLORATORY INVESTIGATION OF THE EFFECT OF MEPROBAMATE ON STUTTERING BEHAVIOR. *L. M. Di Carlo, Jack Katz and Stanley Batkin* 558

BRIEF COMMUNICATION.

Norbert Freedman, Leon Warshaw, David M. Engelhardt, Irving J. Blumenthal and Leon D. Hankoff 562

BOOK REVIEWS 566

ACKNOWLEDGMENTS 574

INDEX 575

Information for Authors

Manuscripts and correspondence pertaining thereto should be addressed to the Editor-in-Chief: Dr. Jacob E. Finesinger, The Psychiatric Institute, University of Maryland, Baltimore 1, Maryland.

Manuscripts should be typed double spaced on one side only of 8½ x 11 paper. The original and one clearly legible carbon copy should be submitted.

It is helpful if the author supplies a short title for use as a running head. This should be typed on a separate sheet and be the first page of manuscript. Type the complete title of the article on a second sheet, and the authors' names and affiliations on a third sheet. Type double-spaced on separate sheets: tabular matter, case histories, quotations, formulas, and other subsidiary matter in the text, footnotes, bibliographies, and legends for illustrations. Legends must not be attached to or written on the illustration copy. Positions for tables and figures in the text should be indicated in the margin of the text page.

Manuscripts should be accompanied by two copies of an abstract of 300 words or less

Illustrations should be drawn in India ink on white paper with clear lettering. Photographs should be glossy prints. The title of the article, name of author, and number of the figure should be written with a soft pencil on the back of each illustration, and the top designated.

References should be designated in the text by number in parentheses, e.g., (7). The list headed REFERENCES at the end of the paper should be arranged in alphabetical order and numbered. Abbreviations should follow the style of the Quarterly Cumulative Index Medicus. Examples:

Book reference:

3. Critchley, M. *The Parietal Lobes.* pp. 171–181. Edward Arnold & Co., London 1953.

Journal reference:

11. Rosvold, H. E., Mirsky, A. F. and Pribram, K. H. Influence of amygdalectomy on social behavior in monkeys. J. Comp. & Physiol. Psychol., **47**: 173–178, 1954.

Authors will be charged for alterations in proof in excess of 10 per cent of the original cost of composition and for the cost of engravings in excess of $50.00. One invoice will be sent covering cost of reprints, alterations and engravings.

The editorial office should be notified promptly of any change of address.

Galley proofs are sent to the author, and should be returned with manuscript to the editorial office. A table of cost of reprints, with an order slip, is sent with galley proof.

The Journal of NERVOUS and MENTAL DISEASE

Copyright© 1959 by The Williams & Wilkins Co

THE PSYCHIATRIC INSTITUTE • University of Maryland • Baltimore 1, Maryland

Jacob E. Finesinger, **Editor-in-Chief**
H. A. Robinson, **Managing Editor**
Robert G. Grenell, **Associate Editor**

EDITORIAL BOARD

Robert A. Cleghorn, *Montreal*
Jerome D. Frank, *Baltimore*
Robert R. Holt, *New York*
James L. O'Leary, *St. Louis*
Talcott Parsons, *Cambridge*
Thomas S. Szasz, *Syracuse*

ADVISORY BOARD

Raymond D. Adams, *Boston*
W. Ross Ashby, *Gloucester, England*
Philip Bard, *Baltimore*
Manfred Bleuler, *Burgholzli, Switzerland*
Mary A. B. Brazier, *Boston*
Jean Delay, *Paris, France*
Joel Elkes, *Bethesda*
Angel Garma, *Buenos Aires, Argentina*
Wendell R. Garner, *Baltimore*
Mario Gozzano, *Rome, Italy*
Manfred S. Guttmacher, *Baltimore*
D. O. Hebb, *Montreal*
Ernest R. Hilgard, *Stanford*
Hans Hoff, *Vienna, Austria*
Maxwell Jones, *Sutton, England*
Maurice Levine, *Cincinnati*
Nolan D. C. Lewis, *Princeton*
A. H. Maslow, *Waltham*
Jerome K. Merlis, *Baltimore*
C. J. Munch-Petersen, *Aarhus, Denmark*
J. H. Quastel, *Montreal*
John R. Reid, *Baltimore*
David Riesman Jr., *Chicago*
A. Earl Walker, *Baltimore*
J. R. Wittenborn, *New Brunswick*

SEDATION AND EUPHORIA FOR NERVOUS IRRITABLE PATIENTS

Use **VALERIANETS-DISPERT**

Reg. U. S. Pat. Off.

Each Chocolate Coated Tablet Contains Ext. Valerian (highly concentrated) 0.05 Gm. dispergantized finely subdivided for maximum efficiency

TASTELESS, ODORLESS, NON-DEPRESSANT SEDATIVE and EUPHORIC

VALERIANETS-DISPERT are indicated in cases of nervous excitement and exhaustion, anxiety and depressive states, cardiac and gastrointestinal neuroses, menopausal and menstrual molimena, insomnia.

Dose: 1 or 2 tablets t.i.d. — Bottle of 50 and of 100 tablets

At All Prescription Pharmacies

STANDARD PHARMACEUTICAL CO., INC. • 253 West 26th St. New York 1, N. Y.

For Intestinal Dysfunction

NUCARPON®

Each tablet cont: Extract of Rhubarb, Senna, Precip. Sulfur, Peppermint Oil, Fennel Oil in activated charcoal base.

For making Burow's Solution U.S.P. XIV

WET DRESSING Use

PRESTO-BORO®

(Aluminum Sulfate and Calcium Acetate)

POWDER IN ENVELOPES — TABLETS —

For treatment of Swellings, Inflammations, Sprains

For Pulmonary Conditions

TRANSPULMIN®

3% solution Quinine with 2½% Camphor for Intramuscular Injection.

Garma: PEPTIC ULCER AND PSYCHOANALYSIS

"... Primarily concerned with actual clinical case histories and with the examination of material communicated in psychoanalytic sessions. It is the author's thesis that ulcer patients have a dependence through being in love with someone who does not satisfy them genitally; this factor in turn acts more traumatically upon them because they are often people with a professional activity that demands too much of them and which prevents them from discharging the emotional tension of their conflicts. He then attempts to substantiate this thesis by giving detailed case histories."—*Gastroenterol.*

160 pp. • $6.00

By ANGEL GARMA, *M.D.*, *Buenos Aires, Argentina*

THE WILLIAMS & WILKINS COMPANY

BALTIMORE 2, MARYLAND, U.S.A.

Information for Subscribers

THE JOURNAL OF NERVOUS AND MENTAL DISEASE

AN EDUCATIONAL JOURNAL OF NEUROPSYCHIATRY • FOUNDED IN 1874

Published monthly, two volumes a year. Subscription price $15.00 per year, $15.50 in Canada, and $16.50 foreign and postal union. Subscriptions should be sent to the publisher.

New subscriptions and renewals are entered to begin with the first issue of the year when subscription is received. Should any issue of that volume be out of print when subscription is received, the pro-rata value will be refunded to the subscriber.

Subscriptions should be renewed promptly. The publisher cannot guarantee to supply back issues on belated renewals.

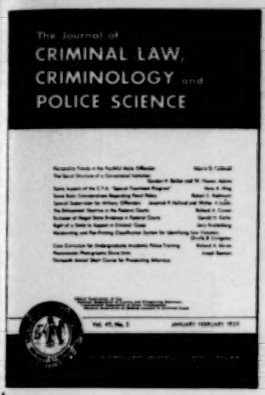
Claims for copies lost in the mails must be received within 30 days (domestic).

Change of address: Publisher must be notified 60 days in advance. Journals undeliverable because of incorrect address will be destroyed. Duplicates can be obtained (if available) from the publisher at the regular price of a single issue ($1.50).

Correspondence concerning business matters should be addressed to the publisher.

THE WILLIAMS & WILKINS COMPANY

Publishers of Scientific Books and Periodicals • **428 East Preston Street, Baltimore 2, Md., U.S.A.**



The Journal of CRIMINAL LAW, CRIMINOLOGY and POLICE SCIENCE

Official publication of The International Association of Arson Investigators, The Illinois Academy of Criminology, the Society for the Advancement of Criminology, and the National Association of County and Prosecuting Attorneys

ROBERT H. GAULT and ORDWAY HILTON, *Editors*

Contents of a recent issue:

Military Justice in the German Air Force During World War II. *Edith Rose Gardner*

Identifying and Treating Potential Alcoholics..... *Roger J. Williams*

Protection of Children Involved in Sexual Offenses: A New Method of Investigation in Israel..... *David Reifen*

A Self Gradient Among Potential Delinquents. *Simon Dinitz, Walter C. Reckless and Barbara Kay*

The Selection of Prison Guards..... *Richard N. Downey and E. I. Signori*

Adults Anonymous: A Mutual Help Program for Inmates and Ex-Inmates. *Albert Eglash*

Self-Incrimination and the Two Sovereignties Rule.

The Role of Common Law Concepts in Modern Criminal Jurisprudence (A Symposium): II. Infamy and the Officeholder.

New Procedures of Scientific Investigation and the Protection of the Accused's Rights..... *Oliver Schroeder, Jr.*

Investigating Automobile Fire Causes..... *Glen A. Shifflet*

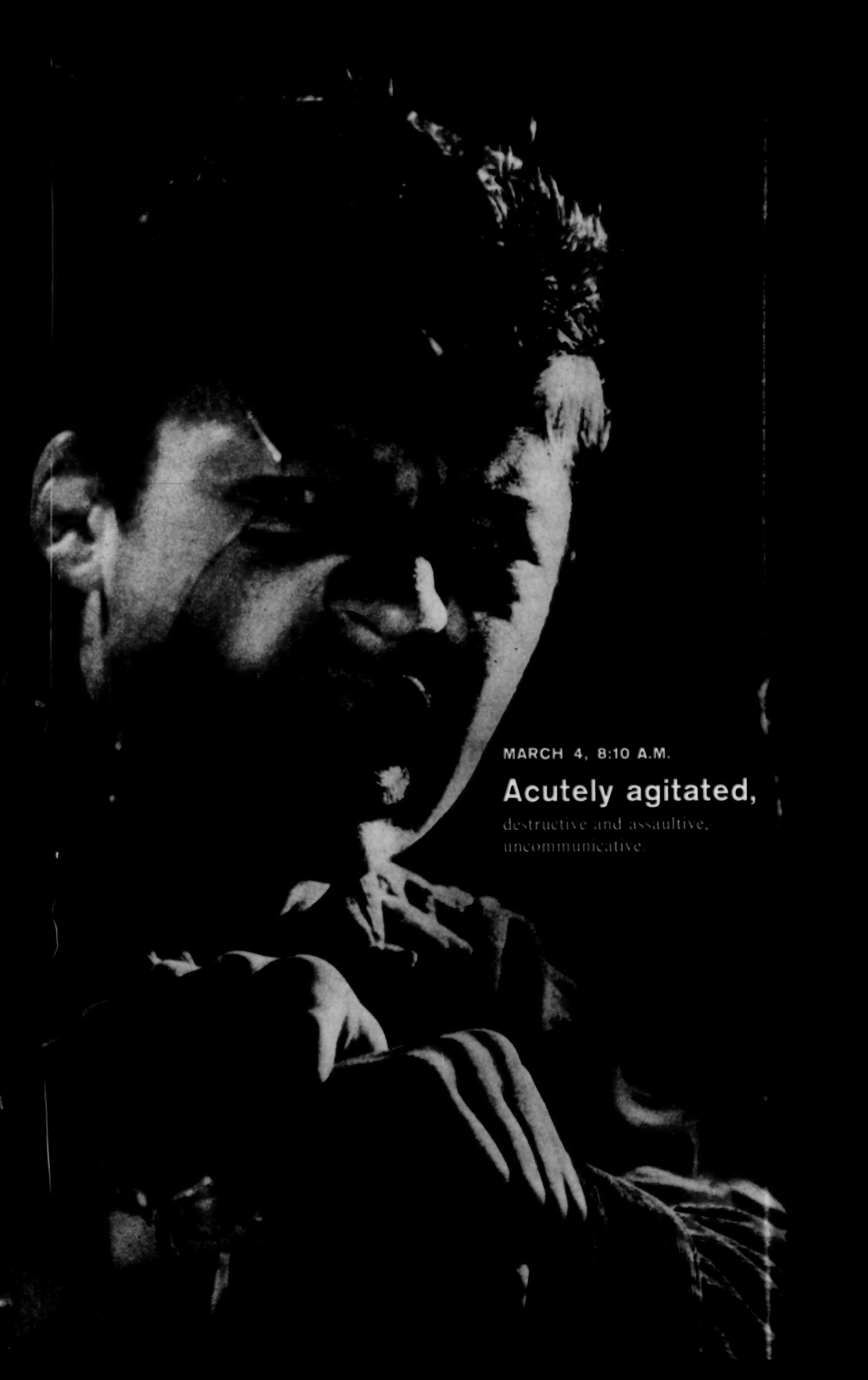
Hit-Run Murders: Examination of the Body..... *Harold L. Beddoe*

Trace Evidence..... *John F. Williams*

Subscription information: Published bimonthly. Subscription price per year: $7.50. Foreign postage: $.75. Canada postage: $.25. Volume 50 current in 1959.

THE WILLIAMS & WILKINS COMPANY

BALTIMORE 2, MARYLAND


MARCH 4, 8:10 A.M.
Acutely agitated,
destructive and assaultive,
uncommunicative.

ARCH 4, 10:00 A.M.
PARINE, I.V., has been given.
atient in light sleep.
an be awakened readily,
d responds to questioning.

MARCH 5, 2:00 P.M.
Receiving oral SPARINE.
Quiet but alert. Contrite
about smashed window.

MARCH 8, 9:00 A.M.
Still on oral
SPARINE, maintenance
dosage. Ready
for psychotherapy.

PARINE quickly controls acute psychotic episodes, then maintains ontrol while definitive psychiatric treatment is provided. SPARINE cilitates accessibility, speeds rehabilitation, simplifies care.

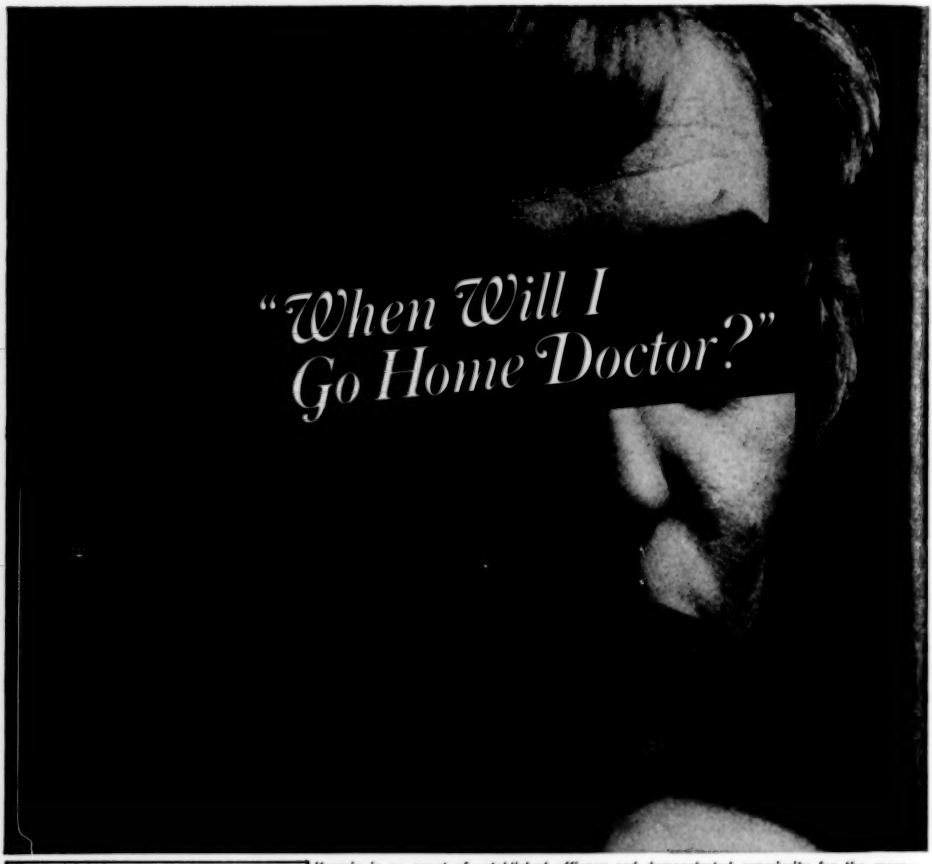
PARINE acts most rapidly by intravenous injection; for effective aintenance, the oral or intramuscular route is usually used. It is ell tolerated in all three methods of administration. *Comprehensive terature supplied upon request.*

Sparine® HYDROCHLORIDE

romazine Hydrochloride, Wyeth

NJECTION TABLETS SYRUP

Wyeth
Philadelphia 1, Pa.



YOUR ANSWER MAY BE "I DON'T KNOW" OR "VERY SOON."

VESPRIN MAY MAKE THE DIFFERENCE

Vesprin is an agent of established efficacy and demonstrated superiority for the management of psychotic patients. In schizophrenia, manic states, and psychoses associated with organic brain disease, Vesprin controls intractable behavior patterns making patients more accessible to psychotherapy. Excitement, panic, delusions, hostile behavior are moderated to permit early insight for rapid progress into resocialization and rehabilitation. Not only is Vesprin your drug of choice for initial therapy, but it has proved effective in patients who failed to respond to other phenothiazines.

Vesprin does not oversedate your patients into sleepiness, apathy or lethargy — and drug-induced agitation is minimal.[1] It is relatively free from side effects.[1,2] Skin eruptions, photosensitivity or hyperthermia have rarely been reported. Individual dosage levels are easily established. Intramuscular injection causes no pain or tissue irritation. Vesprin often brings improvement in chronically disturbed patients refractory to shock therapies and other drugs.[3,4]

VESPRIN

SQUIBB TRIFLUPROMAZINE HYDROCHLORIDE

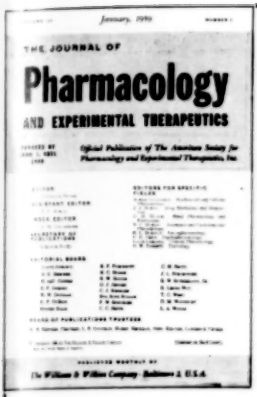
...a unique halogenated phenothiazine for the management of schizophrenia, manic states, psychoses associated with organic brain disease, senile psychoses, and primary behavior problems in children.

Dosage: Usual initial dose, 100 to 150 mg. daily, increased or decreased according to patient response. See literature. Supply: Tablets: 10, 25 and 50 mg., in bottles of 50 and 500. Capsules: 100 mg. in bottles of 50 and 500. Emulsion: 30 cc. dropper bottles and 120 cc. bottles (10 mg./cc.). Parenteral Solution: 1 cc. multiple dose vial (20 mg./cc.) and 10 cc. multiple dose vial (10 mg./cc.). Vesprin Injection Unimatic (15 mg. in 0.75 cc.).

SQUIBB Squibb Quality — the Priceless Ingredient

"VESPRIN" AND "UNIMATIC" ARE SQUIBB TRADEMARKS

1. Goldman, D.: Am. J. M. Sc. 235:67 (Jan.) 1958. 2. Morehouse, W. G., and Freed, J. E.: Monographs on Therapy 3:32 (May) 1958. 3. Leger, Y.: Union Med. Canada 87:831 (July) 1958.
4. Bruckman, N. S.; Saunders, J. C., and Kline, N. S.: Monographs on Therapy 3:24 (May) 1958.



THE JOURNAL OF

Pharmacology

AND EXPERIMENTAL THERAPEUTICS

Official Publication of The American Society for Pharmacology and Experimental Therapeutics, Inc.

LAWRENCE PETERS, *Editor*

Contents of a recent issue:

The Distribution, Excretion and Metabolism of C^{14}-Labeled Tripelennamine (Pyribenzamine) by Guinea Pigs. E. O. Weinman and T. A. Geissman

Studies on the Metabolic Degradation of Propoxyphene. Henry M. Lee, Earl G. Scott and Albert Pohland

Localization of the Site of Action of Chlorothiazide by Stop-Flow Analysis. Arthur J. Vander, Richard L. Malvin, Walter S. Wilde and Lawrence P. Sullivan

Pharmacology of Stereoisomers of 1-Methyl-5-(1-Methyl-2-Pentynyl)-5-Allyl-Barbituric Acid. William R. Gibson, Wilbur J. Doran, Wallace C. Wood and Edward E. Swanson

Effects of Various Centrally Acting Drugs on Fighting Behavior of Mice. Ralph E. Tedeschi, David H. Tedeschi, Anna Mucha, Leonard Cook, Paul A. Mattis and Edwin J. Fellows

The Effects of Meprobamate and Pentobarbital upon Cortical and Subcortical Responses to Auditory Stimulation. Milton Kletzkin and Karl Swan

Effects of Some Steroid and Nonsteroid Lactones on Potassium Exchange and Physiological Properties of the Isolated Perfused Guinea Pig Ventricle. Robert L. Vick

Studies on Veratrum Alkaloids. XXVIII. The Action of the Erythrophleum Alkaloids on the Single Twitch and on the "Veratrine Response" of the Sartorius Muscle of the Frog. Werner Flacke

The Supersensitivity Caused by Cocaine. U. Trendelenburg

Action of Tricyclamol Sulfate on Gastric Secretion of Rats and Dogs. T. M. Lin, R. S. Alphin and K. K. Chen

The Pharmacological Actions of Oxypanamine, an Alkaloid Derived from the Seeds of *Ormosia Panamensis*. Neil C. Moran, Gertrude P. Quinn and William M. Butler, Jr.

An Analysis of the Histamine-Like Actions of Oxypanamine. Neil C. Moran, Gertrude P. Quinn and William M. Butler, Jr.

Subscription information: Published monthly. Subscription price per year: $24.00. Foreign postage: $2.25. Canada postage: $.75. Volumes 125–126–127 current in 1959.

THE WILLIAMS & WILKINS COMPANY

BALTIMORE 2, MARYLAND

NEW THERAPY...TO DEFEAT THE MIGRAINE PARADOX*

'MIGRAL'®

TRADEMARK

- relieves headache
- dispels visual disturbances

and • overcomes nausea and vomiting

*The paradox of migraine – increased nausea due to ergotamine administration – may now be successfully combated with 'Migral'. The recognized benefits of ergotamine and caffeine in 'Migral' are favorably enhanced by the addition of cyclizine hydrochloride, a specific to overcome nausea.

Dosage: 2 to 3 tablets at first warning of an attack, then 1 or 2 tablets every half hour; not more than 6 tablets should be taken for any single attack.

Supplied: 'Migral' tablets, containing ergotamine tartrate 1 mg., 'Marezine'® brand Cyclizine Hydrochloride 25 mg., and caffeine 50 mg.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

9362

E
K*

d-
ne
or-
to

alf

nd

York